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THE FOOD REQUIREMENTS OF CHILDREN *

III. FAT REQUIREMENT

L. EMMETT HOLT, M.D., AND HELEN L. FALES

NEW YORK

The proper amount of fat which is required in the diet during growth has not been and cannot be established since the exact rôle of fat has not yet been determined. Until recently it has been generally supposed that fat did not play any specific part in nutrition, but like carbohydrate, served as a source of energy and as a sparer of protein. In fact, many observers have believed that fat and carbohydrate are practically interchangeable in the diet. Because of this belief little attention has been given to the amount of fat which is desirable in the diet, except in the case of infants. Recent investigations, however, have shown that fat is of greater importance than was formerly believed and that it has specific functions quite apart from those which it shares with the carbohydrates. It has been shown that especially during growth fat is essential. There are now admitted to be several reasons for regarding fat as an important constituent of the diet of children.

FUNCTIONS OF FAT

Fat is the purveyor of the fat soluble vitamin which has been proven to be essential for health and normal growth. A fuller discussion of this particular vitamin will be taken up later with the general subject of food accessory substances. How much of this vitamin should be provided for the child is not yet known. No one of the vitamins has as yet been isolated, consequently the chemical nature and composition of them are unknown. It is, therefore, only possible to express the vitamin content of the different foodstuffs in a relative way, that is, by comparing the value of any one food with some other used as a standard. For example, cod liver oil is used as a standard of comparison for foods containing the fat soluble vitamin A, while yeast serves as the standard for those containing the water soluble B and orange juice for those containing the antiscorbutic or vitamin C. The vitamin content of most articles of food is, however, not constant but

* Received for publication, Feb. 7, 1922.

* From the laboratories of the Rockefeller Institute for Medical Research, and the Babies' Hospital.

is influenced by a number of conditions. For example, summer milk from pastured animals has been shown to have a much higher vitamin content than winter milk from stall fed animals which received no fresh fodder.

In view of these facts it is not possible as yet to state how much fat should be given to a child in order to supply an adequate amount of fat soluble vitamin. From the evidence which has been obtained it seems quite possible that the amount of fat needed for this purpose is comparatively small. However, in order to insure normal growth, it is safer to supply generous amounts of the fats known to contain this substance. The fat soluble vitamin is most abundant in cod liver oil. Among the usual foodstuffs the richest sources are milk fats, egg yolk and certain animal organs—liver, kidneys, etc. This vitamin is also found in the leafy vegetables, but, since a child can take only a comparatively small quantity of these in the diet, it is not wise to depend on them as a source of vitamin to any great extent.

Since the function of these food accessory substances has been appreciated, there has been a growing tendency on the part of those particularly interested in them to regard the fat of the diet of special importance only as a carrier of the fat soluble vitamin. These investigators seem inclined to attribute all the bad effects of a diet low in fat to vitamin deficiency. The fact that a diet deficient in fat predisposes to rickets, that it increases the susceptibility to infection and that it retards growth is explained by them to be a result of avitaminosis. The contention is that if sufficient fat soluble vitamin is supplied in a diet which is fat free, but otherwise adequate, the conditions just mentioned will not develop.

Most of the conclusions regarding the functions of vitamins have been drawn from experiments on small laboratory animals, chiefly rats. Mendel and Osborne [1] have recently published the results of experiments in which they obtained normal growth in rats on a diet extremely low in fat, but which included the necessary amount of the fat soluble vitamin, supplied in their experiments by dried alfalfa leaves. They conclude that "if true fats are essential for nutrition during growth the minimum necessary must be exceedingly small."

To apply dogmatically to human beings the results of experiments on small animals—such as rats, which are of a species so different—seems open to question. The natural diet of the rat is very different from that of the human and consequently its digestive processes may not be entirely comparable. Hence, it is conceivable that fat may have functions in human nutrition, quite apart from that as a purveyor of vitamin A, which may not be required of it in the nutrition of the rat.

1. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **45**:145 (Dec.) 1920.

Von Gröer [2] has observed the effects of a diet practically fat free on two infants from birth. The food given was centrifugalized cow's milk containing only 0.01 per cent of fat with the addition of sufficient cane sugar to raise the carbohydrate content to about 8.5 per cent. of the food mixture. This diet was not only practically devoid of fat, but also extremely low in fat soluble vitamin and high in carbohydrate. Both the infants observed gained in weight with fair regularity for six months, one at the rate of 15 gm. per day and the other at the rate of 20 gm. per day. After six months the gain ceased in both. Both developed rickets and were susceptible to infection throughout the period of observation. The conclusion reached by Von Gröer is that for at least the first six months of life infants can be nourished successfully on a diet which is practically fat free, provided the calories needed are supplied by sugar. His results hardly bear out this contention.

Another function of fat which is questioned by some is its influence on mineral metabolism. This has been much debated and the subject cannot be regarded as entirely settled. Many laboratory observations have been made to ascertain the influence of the fat intake on the mineral metabolism of infants and very young children. Unfortunately, the results thus far have been contradictory and definite conclusions have not yet been reached. This is probably due to the inadequacy of the data.

Although some investigators are convinced that there is no relation between the fat intake and the mineral metabolism, we feel certain that in the case of calcium metabolism at least a very definite relation exists. The work on calcium metabolism done in this laboratory indicates that proper calcium absorption does not usually take place unless the fat in the diet bears a certain relation to the calcium and unless the intake of both is liberal. Our results indicate that the daily fat intake of children from 2 to 4 years of age should not be less than 3 gm. per kilo to insure proper absorption of calcium. This requirement seems to diminish up to 6 years of age to about 2 gm. per kilo, but is probably maintained at about this figure throughout the remainder of childhood. Since adequate absorption of calcium is necessary for bone growth, this need seems a very important one. Our results show that for the purpose of calcium absorption either animal or vegetable fat will serve equally well.

Some authors have recently taken the ground that the fat of the diet has an important influence on the metabolism of protein. Maignon [3] has discussed this question rather fully. He believes that without a proper proportion of fat in the diet the protein is not economically

2. Von Gröer, F.: Biochem. Ztschr. **97**:311, 1919.

3. Maignon, A.: Ann. de méd. **7**:280, 1920; Compt. rend Soc. de biol. **82**: 400, 1919.

utilized, and also that under these conditions protein forms toxic products which may be distinctly harmful. He considers that the amount of fat in the diet should not be regarded as supplementary to the dietary requirement but an integral part of it. Maignon regards as significant the fact that both in cow's milk and in woman's milk the fat exists in greater amount than the protein.

Orgler [4] believes that, although the exact function of fat has as yet not been determined, the lack of fat certainly predisposes to edema and increases susceptibility to infection, especially to tuberculosis. This belief is quite generally accepted. Although children may apparently do well for a time on a low fat or a fat free diet, it is Orgler's opinion that a digestive upset almost inevitably follows. He considers that the complete elimination of fat from the diet or even its reduction to insignificant proportions, as proposed by Pirquet in connection with his new system of feeding, is a hazardous experiment.

It is unquestionable that a reasonable amount of fat in the diet is of service in maintaining normal conditions in the intestine. This is indicated by observations on the character and composition of stools. Stools which would be generally regarded as normal in character and consistency are not found when for a considerable time the fat of the diet has been excluded entirely or reduced to a very small amount. Only a small proportion—usually about 5 per cent.—of the ingested fat is not absorbed, but this small amount has, we believe, as Hutchison [5] recently suggested, "a function to perform and is not a pure excretion." The fat excreted is largely in the form of soap which gives solid consistency to the stools. Again, the reaction of the stool is to a great extent dependent on the relative proportions of fat and carbohydrate in the diet. When carbohydrate forms too large a proportion of the diet, the acidity of the stool is regularly increased. When, however, there is sufficient fat in the diet to supply a normal amount of soap in the stool there is no excessive acidity. Consequently, the fat in the diet may be regarded as exerting on the mucous membrane of the intestine a protective action against the irritating effects which may be produced by fermentation of carbohydrate when this element is given in excess. This will be considered more fully in discussing carbohydrate requirement.

Aside from these reasons for regarding fat per se as an important constituent of the diet of the child, it must not be forgotten that fat as a source of energy provides more than twice as many calories per gram as does either protein or carbohydrate.

From the foregoing it seems quite clear that a considerable amount of fat is desirable and probably essential for the best nutrition of the

4. Orgler, A.: Deutsch. med. Wchnschr. **46**:290 (March 11) 1920.
5. Hutchison, H. S.: Quart. J. Med. **13**:277 (April) 1920.

growing child. The exact quantity needed, however, is difficult to determine. At the present time it can only be conjectured. Many authorities think that the diet naturally chosen is an indication of a physiologic need.

FAT IN THE DIET OF INFANTS

That fat is a natural component of the diet of the infant is shown by the composition of woman's milk. The normal amount of fat in woman's milk, on the average between 3 and 4 per cent., furnishes approximately half the total calories in the diet of the nursing infant. This cannot be without great significance. It seems hardly conceivable that so much fat would be supplied by nature if the only specific purpose of the fat were to furnish the vitamin. The nursing infant usually receives during the early weeks about 20 gm. fat daily. This increases to an average of about 40 gm. daily at the sixth or seventh month. This represents about 4 gm. per kilo of body weight.

Nature provides fat generously not only for the nursing human infant but also for the young of all mammals. The various milks all contain a considerable proportion of fat; in many of them the fat occurs in greater proportion than in woman's milk. In most milks the amount of fat and protein run almost parallel, but in several the fat considerably exceeds the protein.

The infant fed on modifications of cow's milk does not usually receive as much fat as does the nursing infant. The complete digestion of the fat of cow's milk is difficult for many infants. Consequently, it must be given in smaller amounts and increased cautiously. A widely accepted basis for the artificial feeding of the average normal infant is an allowance of 1.5 ounces of cow's milk for each pound of body weight. The fat intake calculated on this basis ranges from 15 gm. daily during the early weeks to 35 gm. daily at one year. This provides about 3.5 gm. fat per kilo of body weight. The fat allowance for different infants varies rather widely according to the individual capacity to digest cow's milk fat. Many pediatrists are inclined to attribute most of the digestive disturbances of infants to the fat of the diet and to recommend the more extensive use of skimmed milk formulas. Others consider a more liberal intake of fat to be of great advantage to most healthy children and use whole milk or in certain cases top milk of varying degrees as the basis for the milk modifications.

FAT IN THE DIET OF OLDER CHILDREN

Although there are in the literature many statements regarding the amount of fat recommended for children after infancy, there are but few actual records of the amount of fat taken in individual cases and few observations as to the effects of either a very high or a very low

fat intake. The amount of fat taken by more than one hundred normal children studied by us may, perhaps, be regarded as typical of that usually taken by healthy children.

Total Fat Daily.—The total daily amount of fat which these children received in their diet is shown in Chart I. The lines represent the grams of fat daily which would supply 35 per cent. of the total calories recommended by us in a previous paper.[6] As will be shown later, healthy children take on the average about 35 per cent. of their total daily calories as fat. It will be seen that there is considerable variation in the individual values. However, there is a notable tendency to follow the lines indicated. Most of the instances of very high fat intake were in children of extreme activity. Two boys in their fifteenth

AVERAGE FAT INTAKE OF NORMAL CHILDREN

Age, Years	Boys			Girls			Both Sexes		
	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.
1–2	2	36	3.7	5	36	3.2	7	36	3.3
2–3	4	42	3.1	7	53	3.9	11	49	3.6
3–4	6	44	3.2	4	64	4.1	10	52	3.6
4–5	7	57	3.3	5	58	3.2	12	57	3.3
5–6	5	63	3.2	5	59	3.4	10	61	3.3
6–7	4	78	3.4	4	55	2.8	8	66	3.1
7–8	2	88	3.5	3	73	2.9	5	79	3.1
8–9	4	92	3.4	5	82	2.9	9	86	3.1
9–10	5	101	3.5	4	70	2.6	9	87	3.1
10–11	6	99	3.2	3	68	2.0	9	89	2.8
11–12	3	106	2.7	1	81	2.2	4	100	2.6
12–13	1	118	2.6	2	87	1.9	3	97	2.1
13–14	0	...	...	1	83	1.6	1	83	1.6
14–15	2	152	2.7	1	70	1.5	3	124	2.4
15–16	2	142	2.4	1	117	2.2	3	134	2.3
16–17	1	121	2.5	0	...	...	1	121	2.5
17–18	0	...	...	1	101	1.8	1	101	1.8

and sixteenth years, respectively, took more than 150 gm. fat daily. This large amount is indicative of the needs and habits of adolescence.

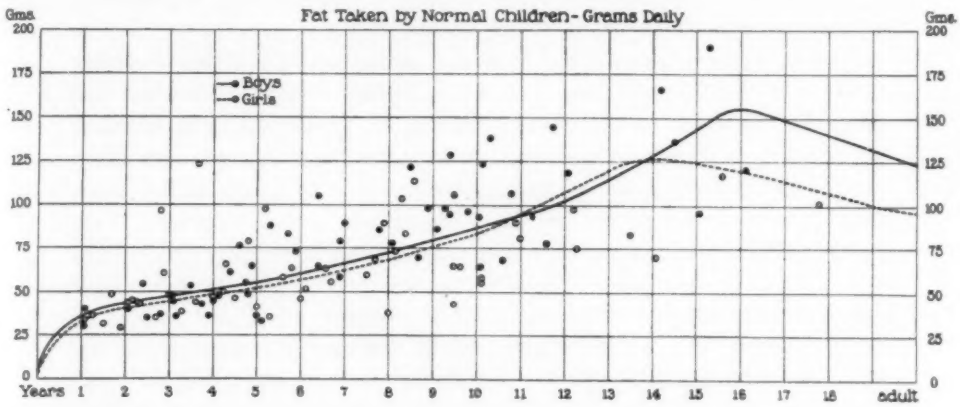
In the accompanying table are shown the average values according to years for total fat intake of the cases studied. The average values are given for boys and girls separately as well as for both sexes together. There is a practically steady increase in the average intake, reaching a maximum during the fifteenth and sixteenth years, as would be expected. The boys show a rather higher average intake than the girls.

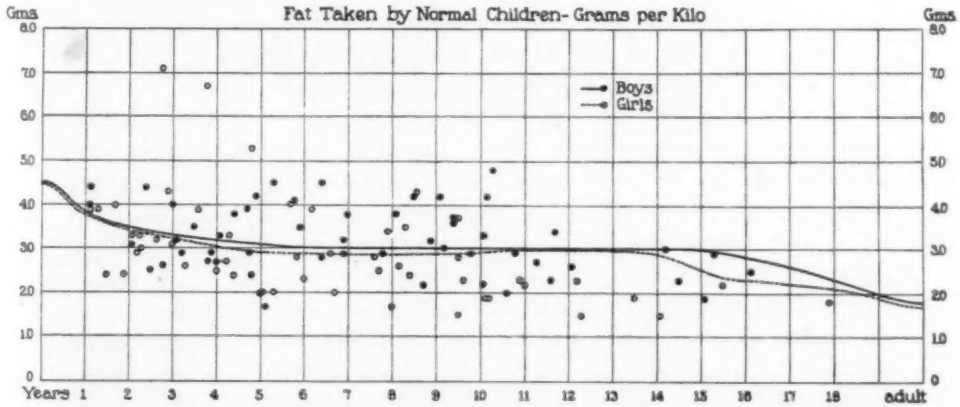
Fat Per Kilo.—The individual values for the grams of fat per kilo taken by these children are shown in Chart 2. Although there is a considerable variation in the values, more than three-fourths of the children took between 2 and 4 gm. per kilo daily. The amounts taken by the boys show less variation than do those by the girls. The girls

6. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child. **21**:1 (Jan.) 1921.

with very high intake were all healthy but extremely active children. The chart shows that as age advanced there was a gradual reduction in the grams of fat taken per kilo.

The average values for grams of fat per kilo, shown in the table, are nearly the same for both sexes during the early years—a little more than 3 gm. per kilo. Between the ages of 6 and 11 the values for the boys average a little more than 3 gm. per kilo; those for girls are





somewhat lower. After the age of 11 there are too few data to warrant conclusion.

Müller [7] found the average fat intake of thirty-two children from 2 to 6 years of age to be 3.45 gm. per kilo, both sexes being grouped together. This value agrees with our findings for corresponding ages. Most of the other observations reported by German authors show lower values. Those of Camerer, who has been widely accepted as

7. Müller, E.: Biochem. Ztschr. **5**:143, 1907.

an authority, are especially low, most of his values being less than 1.5 gm. per kilo. In his recommended schedule the fat allowance is only about one-half that which is usual in the diet of American children. Among the authors who have proposed a scheme of feeding in which exact quantities of the food constituents are given. Steffen [8] is about the only one who recommends a generous fat intake. Pirquet [9] has taken the position that fat is not a fundamentally essential article of diet and that it can be largely, if not entirely, replaced by carbohydrate without harm to the organism.

An important recent report on the amount of fat taken by older children is that found in the article by Gephart,[10] who studied the diet taken by the boys of St. Paul's School, to which we have referred previously. These boys took on the average about 200 gm. fat daily. Of the three groups, the youngest, averaging 13½ years of age, took an average of 4.5 gm. fat per kilo; the middle group, averaging 14½ years, took 3.9 gm. fat per kilo; the older group, averaging 16½ years, took 3.4 gm. fat per kilo. These values are much higher than has been thought desirable for those ages. The average adult diet, based on many observations, contains only about one-half the amount of fat taken by these boys. Gephart's findings, however, are in accord with our belief that the food needs during adolescence considerably exceed those of adult life. The fact that the fat intake of so many healthy boys was so high is undoubtedly significant. This large amount of fat apparently had no deleterious effect; on the contrary, the boys thrived and it seemed to represent a physiologic need.

Certain clinicians are inclined to attribute many of the common digestive disturbances seen in older children to the fat in the diet, particularly the fat of cow's milk. It is undoubtedly true that under certain conditions a very high intake of fat, especially when accompanied by a great reduction in the carbohydrate intake, may bring about disturbances of digestion. The characteristic symptoms are coated tongue, bad breath, general malaise, constipation, with large gray stools containing a high proportion of fat, and sometimes severe and prolonged attacks of vomiting. In many such cases, however, when fat is blamed, the real cause of disturbance is too much food. This is apt to occur when children of limited activity are given more than a quart of milk, and that often rich milk, in addition to liberal amounts of solid food. It is important before lowering the fat intake to consider the diet as a whole, especially as to the total amount of food taken and the relative amounts of fat and carbohydrate which the diet contains. There is evidence that when a diet is properly balanced, that

8. Steffen, W.: Jahrb. f. Kinderh. **46**:332, 1898.
9. Pirquet, C.: System der Ernährung, Berlin, 1917.
10. Gephart, F. C.: Boston M. & S. J. **176**:17, 1917.

CONCLUSIONS

In the cases of spasmophilia in the infants studied, no evidence of "alkalosis" was found. In fact, there was a tendency for the alkali reserve to be lowered during the spasmophilic stage and gradually to be increased as the cases recovered.

It appears that the symptoms of tetany may be produced in a variety of ways, but the evidence is not forthcoming that "alkalosis" plays a part in the genesis of infantile spasmophilia.

We wish to thank Dr. Welker and the Department of Physiological Chemistry of the University of Illinois for the privilege of using their laboratories for the blood chemistry work.

is, contains the fat, protein and carbohydrate in the right relation to each other, very much larger amounts of fat can be tolerated than when the diet is unbalanced.

Whenever the fat in the diet is much reduced it is necessary in order to supply sufficient calories to greatly increase the carbohydrate. When this is done there is always great danger of disturbing digestion from an excess of carbohydrate.

While it may not yet be established that a large amount of fat is essential in the diet during growth, there are so many reasons for a liberal allowance of fat and so little evidence that this is harmful to children with normal digestion that it does not seem wise with our present knowledge to reduce the fat much below the amount which healthy children usually take, while to exclude it entirely from the diet seems quite unjustifiable and hazardous.

SUMMARY

1. Many of the functions of fat in the diet are still subjects of debate.

2. A certain amount of fat should be supplied to provide fat soluble vitamin. This amount is not yet known. It may be exceedingly small, but until this is known it seems wise not to reduce the fat supply greatly lest there may be a deficiency in vitamin A.

3. Fat probably has an important influence on mineral metabolism, especially on calcium metabolism. For the best absorption of calcium we have found it desirable to supply as much as 3 gm. fat per kilo in the early years and as much as 2 gm. per kilo after 6 years.

4. Fat is probably necessary for proper digestion and utilization of protein and on this account it seems desirable to supply as much fat as protein in the diet.

5. Fat helps to maintain normal physical, bacteriologic and chemical conditions in the intestine. It also exerts a protective action against the irritating effects of the products of carbohydrate fermentation.

6. A great reduction of fat in the diet increases the susceptibility to infection, especially to tuberculosis.

7. The nursing infant receives a generous amount of fat, usually as much as 4 gm. per kilo daily.

8. The infant taking modifications of cow's milk usually receives about 3.5 gm. fat per kilo daily.

9. Older children studied by us took on the average over 3 gm. fat per kilo daily when under 6 years of age and about 3 gm. per kilo during the remainder of the growth period.

10. The grounds for the current impression regarding the harmful effects of fat on children should be investigated carefully. There is little evidence that a liberal amount of fat in the diet is harmful to

children with normal digestion and much evidence that fat is an important and necessary component of the diet during the entire growth period.

11. In general, it seems rational to supply in the diet of the child as much as 4 gm. fat per kilo daily at one year, decreasing the amount to about 3 gm. per kilo at 6 years and maintaining this value throughout the remainder of the growth period.

THE FREQUENCY OF TUBERCULOSIS IN CHILDHOOD*

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STYRIA, AUSTRIA

In collaboration with Monti,[1] I found that 95 per cent. of the children of the poor in Vienna showed evidence of a tuberculous infection at the time of puberty. Since then a number of papers on this subject have appeared from various cities and countries. The results were very different. The cause of this variation lies partly in the actual differences in the various cities, but to a certain extent the difference in the method used for the examination and the difference in the selection of the material share the responsibility.

I regard it necessary that the important question of the spread of tuberculosis in definite cities, countries and strata of society should be answered definitely. To this end it is absolutely necessary to use the best methods of examination and to select the material properly.

SELECTION OF MATERIAL

A true picture of the actual conditions can only be obtained by examining either all children of a certain age, or all children, which is hardly possible. The examination of school children means a selection which can be regarded as free from objection and so does the examination of children attending public kindergartens. The examination of children in infectious disease hospitals can also be used because it is permissible to assume that children with or without tuberculosis acquire diphtheria or scarlet fever with equal readiness. Figures obtained in a scarlet fever or diphtheria ward surely may be regarded as representative of the actual conditions, but it is not permissible to use results obtained in a dispensary for the preparation of statistics. This material includes many more tuberculous children than the average. Tuberculous children tend to concentrate there and the figures become too high. For this reason the figures which Von Pirquet gave in his first statistic based as they were on the material of the dispensary of the Vienna Kinder Klinik cannot be accepted; and many contributions of other investigators share this fate.

TUBERCULIN METHOD

It is not sufficient to exercise proper care in the selection of the material but the tests have to be made with a reliable method. Only

* Received for publication, March 18, 1922.

1. Hamburger and Monti: München. med Wchnschr. **56**:450, 1909. Monti: Wien. med. Wchnschr. **62**:447, 1912; Wien. klin. Wchnschr. **21**:1407, 1908.

then can the frequency of tuberculosis be established. The justification of such a demand is self-evident. Nobody will doubt its principle in the least. In spite of this many papers dealing with the frequency of tuberculosis in different cities and countries reveal the fact that, quite generally, a tuberculin method has been used which is entirely unreliable, having an error as high as 40 per cent. This method is the cutaneous tuberculin test of Pirquet. The main purpose of this paper is to call attention to the fact that this method is inexact and therefore misleading. It gives figures which are far too low.

The method of Pirquet is very simple. It rapidly gained great favor and was used widely. Many papers are published which are based entirely on the Pirquet method, but the results are wrong because the method is inexact. Twelve years ago, Reuschel,[2] and shortly afterward I, called attention[3] to this fact. It was shown that the local subcutaneous reaction (so-called Stichreaction) gives much more reliable results. I have called attention again and again to this unreliablity of the Pirquet reaction and particularly in my monograph on tuberculosis in childhood, but, I regret to say, without much success.

A comparison of the figures obtained by Pirquet with his cutaneous method with those obtained by Monti and myself with the local subcutaneous method demonstrates the degree of error of the cutaneous reaction. Vienna furnished the material for both statistics. Pirquet found in children from 11 to 14 years of age an incidence of tuberculosis of only 56 per cent.; we found 95 per cent., i. e., 40 per cent. more. At that our figures were obtained from a material (hospital for infectious diseases) in which rather less tuberculous infection was to be expected than in the material of Pirquet (dispensary). Only very few authors confirmed the statements of Reuschel and myself (Nothmann,[4] Pirquet,[5] Rominger[6]). Occasionally the intracutaneous method of Mantoux has been employed, but not frequently. This method has no advantages over the subcutaneous method and at times the dosage remained insufficient. In order to exclude tuberculosis, the reaction must remain negative with from 1 to 10 mg.

The method I worked out in detail is this: All children to be examined are first subjected to a cutaneous or percutaneous test with concentrated tuberculin.[7] Those who do not react, from twenty-four to forty-eight hours later, receive a subcutaneous injection of 0.01 mg.

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2. Reuschel: München. med. Wchnschr. **55**:330, 377, 1908.
3. Hamburger: Wien. klin. Wchnschr. **21**:381, 1908.
4. Nothmann: Berl. klin. Wchnschr., 1910, No. 9.
5. Pirquet: Ergebn. d. inn. Med. u. Kinderh. **5**:
6. Rominger: Monatschr. f. Kinderh. **18**:424, 1920.
7. With the percutaneous inunction method of Moro more positive results are obtained if the original tuberculin is evaporated on the waterbath ad maximum (F. Hamburger and F. Stradner: München. med. Wchnschr. **45**:243 [Feb. 27] 1919).

tuberculin. Those who do not react after the second injection are given a third injection after a further twenty-four hours. If the test is negative, another injection is given after the lapse of another twenty-four hours, or at most forty-eight hours, the dosage being raised to 1 mg. If the place of injection does not show any reaction, such as definite redness and infiltration, the child may be regarded as free from tuberculosis with nearly absolute certainty. In doubtful cases, an injection of 10 mg. is given.

It is evident that this method is time consuming and bothersome. In schools and similar public institutions it meets with opposition. The cutaneous or percutaneous method, on the other hand, is very simple in its execution and does not meet with opposition. A cumbersome method of examination competes with a simple one, but the cutaneous method is absolutely unreliable and the subcutaneous method is reliable. It cannot be the object of scientific investigation to find out how many individuals of a given age give a positive cutaneous reaction, but solely how many children of a given age are infected with tuberculosis. The cutaneous method cannot be used comparatively on the assumption that the percentage of its error remains constant. The results of this method are too dependent on a variety of circumstances: (1) The kind of instruments used (Pirquet's "Bohrer," scalpel, vaccination lancet, needle) and the depth of the wound. (2) The length of time the tuberculin acts. (3) The activity of the tuberculin. The different series of the same firm have by no means a constant activity. (4) Whether the cutaneous test has been made once or repeatedly. In the latter case more positive results are obtained. (5) The time of the year seems to exercise some influence on the reaction.[8]

Sufficient data, I believe, have been given to show that the cutaneous reaction cannot alone be used to determine the frequency of tuberculosis. The cutaneous or percutaneous method should be employed first and only when these reactions are negative the subcutaneous method just described should be used.

SUMMARY

To determine the frequency with which tuberculous infection has occurred in various periods of childhood, it is necessary (1) to select properly the material to be examined. The test can be done in children from schools or kindergartens or from infectious disease hospitals, but not in children from dispensaries. (2) To choose the proper method of applying the tuberculin test. The only suitable method is the subcutaneous injection (from 1 to 10 mg.) after a preceding cutaneous or percutaneous application. The cutaneous or percutaneous method alone cannot be used.

8. Hamburger: München. med. Wchnschr. **67**:398, 1920.

IDIOPATHIC APLASTIC ANEMIA*

REPORT OF CASE IN A CHILD FOUR YEARS OLD; MARKED IMPROVEMENT FROM TRANSFUSION

CHARLES HERRMAN, M.D.

NEW YORK

REPORT OF CASE

M. L., female, aged 4, was admitted to Lebanon Hospital Nov. 4, 1921.

Family History.—Parents apparently healthy; no history of tuberculosis or syphilis; no members of the family have had any diseases of the blood or the blood forming organs. Patient has one sister who is healthy.

Personal History.—Full term, normal delivery; breast fed; normal physical and mental development during infancy. Measles at 2 years of age, no complications.

Present Illness.—During the past two weeks she has had fever, has become more and more pale and weak; complained of pain in the abdomen.

Physical Examination.—Child apathetic; marked grayish white pallor; puffiness of the face, especially the eyelids; all the mucous membranes are very pale. Sclera bluish, not yellowish. No distinct enlargement of the lymph nodes.

Heart: No murmur, no marked enlargement; regular but rapid (130).

Lungs: Negative.

Abdomen: Negative; liver and spleen not enlarged.

Extremities: On the back of the left calf is an ecchymotic spot 2 cm. in diameter.

Examination of the Blood.—November 4: hemoglobin (Dare) 25 per cent.; red blood cells, 750,000; white blood cells, 2,500; polymorphonuclears, 25 per cent.; lymphocytes, 72 per cent.; no myelocytes. The red cells show slight changes in form, size and color. No nucleated red cells. The results of the examination of the blood at various times are given in Table 1.

Clinical Course.—As the child appeared to be moribund, she received a transfusion of 380 c.c. blood (father). To our great surprise she rallied, and made a gradual but progressive improvement.

November 7: Distinct improvement, less pallor, apathy and irritability; improvement in appetite. Pirquet and Wassermann tests negative. Examination of fundus (Dr. Barnert): no hemorrhages. Urine: acid; specific gravity, 1.014; trace of albumin; occasional hyaline cast and a few white blood cells; no urobilin. Feces: no blood, parasites, or ova.

ROENTGENOLOGIC EXAMINATION (Dr. Scholz)—Chest: moderate swelling of the root glands; slight increase in upper mediastinal shadow; moderate enlargement of the heart to the left. Arm: increased porosity of the bones, moderate diffuse atrophy.

November 11: Rise in temperature to 106 F., no apparent cause.

November 12: Spleen just palpable.

November 16: Spleen distinctly palpable.

November 14: Rise in temperature to 105.5 F.; no visible cause.

November 16: A large ecchymotic spot appeared on the left side of the neck 3 cm. in diameter.

November 18: Tonsils red and slightly enlarged.

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* Read at the Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 1-3, 1922.

The patient was discharged Dec. 3, 1921, very much improved. In the latter part of December she had a mild attack of tonsillitis from which she recovered without any apparent injurious effect on her general condition or blood.

Name.—In addition to aplastic anemia, a number of different names have been given to this condition by different authors: aregeneratory anemia (Pappenheim); hemolytic aplastic anemia (Turk); aleukie

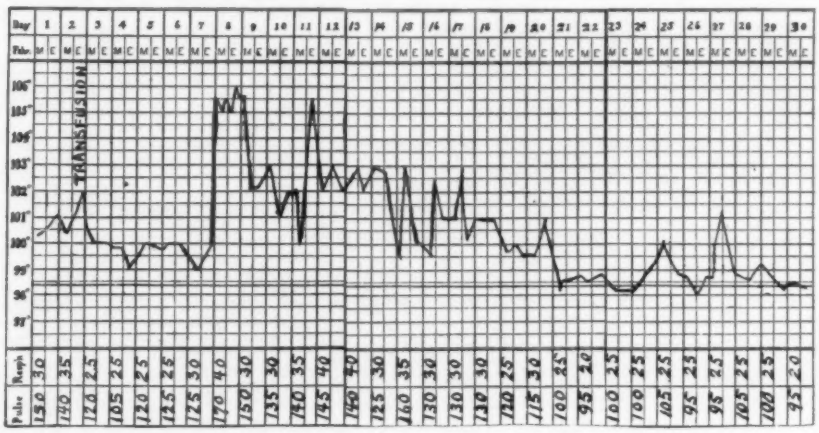

TABLE 1.—Result of Blood Examinations

Date	Hb. per Cent.	R. B. C.	W. B. C.	Polymorphonuclears, per Cent.	Lymphocytes, per Cent.	
Nov. 4, 1921	25	750,000	2,500	25	72	Slight poikilocytosis and polychromatophilia; few macrocytes; no nucleated red cells or myelocytes
Nov. 5, 1921	20	800,000	2,500	..	..	Slight poikilocytosis and anisocytosis; no nucleated red cells or myelocytes
Transfusion Nov. 7, 1921	45	2,330,000	2,400	22	65	Platelets. 170,000; coagulation time, 8 min. (Lee-White)
Nov. 13, 1921	43	2,700,000	2,300	40	55	Bleeding time, 10 min. (Duke); fragility normal; complete, 0.36
Nov. 24, 1921	47	2,500,000	3,500	36	60	Slight poikilocytosis and anisocytosis; no nucleated red cells or myelocytes
Dec. 3, 1921	65	3,800,000	6,000	47	50	

hemorrhagica (Frank). Schneider proposes the terms toxic paralytic anemia and toxic anhemopoietic anemia, because aplastic implies a congenital deficiency, and aregeneratory implies a poorly developed marrow readily failing on demand. However, the term aplastic anemia has been so generally used that it seems best to retain it.

TABLE 2.—Analysis of Cases of Aplastic Anemia in Children

Author	Sex	Age	Duration	Hb., %	R. B. C.	W. B. C.	Polymorphonuclears		Marrow
Acuna	♀	9	1 mo.	..	1,500,000	4,200			
Babonneix and Paisseau	♂	11	6 wk.	25	510,000	4,800	24	Slight anisocytosis and poikilocytosis; no nucleated red cells or myelocytes; few macrocytes	Fatty
Babonneix and Tixier [1]	♀	5	3 mo.	15	380,000	2,000	24	No anisocytosis, poikilocytosis, polychromatophilia, nucleated red cells or myelocytes	
Babonneix and Tixier [1]	♂	11	1 yr.	15	550,000	1,200	34	Slight anisocytosis; no poikilocytosis, polychromatophilia or nucleated red cells	Fatty
Benecke [2]	♂	6	Recovery	12	440,000	1,600	42	Slight anisocytosis; no poikilocytosis or nucleated red cells	
Gorter	♂	6	3 wk.	17	700,000	1,600	12	Anisocytosis; no polychromatophilia, nucleated red cells or myelocytes	Fatty
Herrman	♀	4	Recovery	25	750,000	2,500	25	No anisocytosis, poikilocytosis, polychromatophilia, nucleated red cells or myelocytes	
Heubner	♂	2	6 mo.	10	980,000	7,800	..	Anisocytosis; no poikilocytosis, polychromatophilia or nucleated red cells	Fatty
Kharina [3]	♀	2½	.....	12	630,000	7,800	43	Slight anisocytosis and poikilocytosis	
Kleinschmidt [4]	♀	8	6 mo.	10	1,000,000	3,000	13	No anisocytosis, poikilocytosis or polychromatophilia; few nucleated red cells	Hypoplastic
	♂	10	6 mo.	23	1,200,000	1,800	28		
	♂	12	4 mo.	35	2,000,000	2,800	11	Poikilocytosis; no nucleated red cells	
	♀	4½	21 mo.	22	820,000	5,800	36	.....	Fatty
Larrabee	♂	5	1 yr.	25	1,500,000	5,000	3.2	No anisocytosis, poikilocytosis or nucleated red cells	
Muir	♂	14	3 mo.	12	640,000	7,000	25	Slight poikilocytosis; no nucleated red cells or myelocytes	
Parkinson [5]	♂	9	Recovery	20	580,000	2,600			
Rennie [6]	♀	13	3 mo.	20	720,000	3,800	5	No anisocytosis, poikilocytosis, nucleated red cells or myelocytes	
Silva	♂	12	3½ mo.						
Smith [7]	♂	6	8 mo.	10	400,000	4,000	25	Poikilocytosis; anisocytosis; achromatocyte	Fatty
Spak [8]	♂	4							
Türk	♂	12	4 mo.	11	500,000	4,280	32	Slight anisocytosis, poikilocytosis and polychromatophilia; no nucleated red cells or myelocytes	
Thursfield [9]	♀	11	7 mo.	30	1,140,000	5,200	35	.....	Fatty

1. Babonneix and Tixier: Bull. et mém. Soc. méd. d. hôp. de Paris, **35**:227, 1913.
2. Benecke: Therap. d. Gegenw. **19**:14, 1917.
3. Kharina-Marinucci: La Pediatria **23**:101, 1915.
4. Kleinschmidt: Jahrb. f. Kinderh. **81**:1, 1915.
5. Parkinson: Proc. Roy. Soc. Med. Lon. **11**:55, 1917 (Sect. Dis. Child.); **12**: 72, 1918 (Sect. Dis. Child.).
6. Rennie: Med. J. Australia **1**:485, 1919.
7. Smith: Am. J. Dis. Child. **17**:174 (March) 1919.
8. Spak: Acta Pediatrica **3**:310 (Dec. 15) 1921.
9. Thursfield: Brit. M. J. **2**:873, 1921.

Frequency.—About eighty cases of this condition have been reported. Of these twenty-one occurred in children. However, I have no doubt that with more careful observation and hematologic study the disease will be found to be less rare than the number of reported cases would seem to indicate.

Sex.—About an equal number of cases have occurred in each sex in adults; in children, however, twice as many occurred in males as in females: fourteen males, seven females. Only one case has been reported in an infant, that of Heubner.

Etiology and Pathogenesis.—Although many hypotheses have been advanced, very little is known at present as to the causation of this condition. The most generally accepted explanation is that it is a primary lesion of the bone marrow due to the action on it of some unknown toxic material. This results in a deficient production of blood cells, red cells, polymorphonuclear leukocytes, platelets and myelocytes. There is no definite evidence that the reduction in the red cells is due to increased destruction. The urine is free from urobilin; the skin is not icteric; the serum is not darker than normal in color; in the blood there is usually an absence of poikilocytosis; the color index is rarely above 1. In the liver there is usually no marked deposit of hemosiderin. The family history is usually negative as far as disease of the hemopoietic system is concerned. In only a very few cases is there a history of tuberculosis or syphilis.

In a few the disease has followed an acute infection. Smith considers the possibility in his case that "the prolonged toxic action of the toxin of measles, acting in a cumulative sort of fashion, until the marrow became exhausted" might have caused the condition, but when it is considered that practically all children have measles, that, therefore, even the rarer complications are not uncommon, it seems strange that if aplastic anemia bears some relation to the disease it should be so rare. It would have to be assumed that the particular patient had a congenital or acquired inferiority of the bone marrow. Of course, such an inferiority might be latent, and only brought to light by an attack of some acute infectious disease, such as measles. As a matter of fact, several authors have suggested the possible presence of such an inferiority in these cases, and a few patients were anemic from birth or at a very early age. In two of Schneider's three cases a "status lymphaticus" was found at necropsy.[10] Türk has suggested a possible relation to hypoplasia of the blood vessels and genitals. However, the majority of the patients reported were apparently well until the onset

10. Moore and Keidel noted that secondary apastic anemia following the injection of arsphenamin, was more common in patients with the lymphatic diathesis.

of the disease. Kleinschmidt [4] considered carefully the possible presence of a constitutional peculiarity or inferiority in his patients, but could find no definite evidence.

Pathology.—Characteristic changes are found in the skin, mucous membranes, liver and spleen; and pathognomonic changes in the bone marrow. In the skin petechial hemorrhages or ecchymotic spots of greater or less extent. Hemorrhage from any or all the mucous membranes, and the serous coverings of the viscera. Various organs, principally the heart muscle, liver, kidneys show fatty degeneration. A marked deposit of hemosiderin is rarely found in the liver. The bone marrow is largely replaced by fat and connective tissue, which gives it a yellow color and a peculiar consistency. A small remnant of normal or even compensatory hyperplastic marrow may occasionally be found, but the red color may be due to small hemorrhages. On examination the marrow shows an absence of normoblasts, megaloblasts, and myelocytes, the predominating cells being lymphoid.

Symptomatology.—The disease manifests itself by anemia, shortness of breath and general weakness. The skin and conjunctiva are not yellow; the former is grayish white, the conjunctiva has a bluish tinge. A puffiness of the face, more especially the eyelids is frequently noted. There may be pain in different parts of the body, but there is no definite pain on pressure over the bones. Fever may be present, sometimes marked without discoverable cause.

There is usually a distinct hemorrhagic tendency as shown by the appearance of petechial spots on the skin, and in many cases hemorrhages from various mucous membrane surfaces. Retinal hemorrhages are not uncommon. In many cases a systolic murmur is heard at the base of the heart; no characteristic changes are found in the lungs. The liver, spleen and lymph nodes are not usually enlarged. As a rule, there are no marked nervous symptoms, unless the disease is associated with complications.

The urine does not contain urobilin. Occasionally a trace of albumin, and a few hyaline casts may be present. When there is hemorrhage in any part of the digestive tract the stools will contain blood. Roentgenologic examination of the bones may reveal changes in texture; and with improved technic it is not unlikely that much valuable information will be obtained in this way. In Muir's case there was found at necropsy a thickening of the cortex of the bone, and a diminution in the size of the medullary canal. In my own case there was an increased porosity, as shown by the less dense shadow.

The changes in the blood are characteristic. There is a marked diminution in the percentage of hemoglobin, the number of red and white blood cells. The reduction in the leukocytes is chiefly at the expense of the polymorphonuclears. As a rule, there are no normo-

blasts or megaloblasts and no myelocytes. The form, size and color of the red cells is not usually changed. The number of platelets is diminished, sometimes very markedly. The bleeding time is increased. The coagulation time is normal, but there is an imperfect retraction of the clot. The fragility of the red cells is normal as tested with hypotonic saline solutions. Blood cultures are negative.

The anemia and general weakness, together with the hemorrhagic tendency, usually become progressively worse, and the patients die from asthenia or some intercurrent complication.

Diagnosis.—In a fairly typical case it should be possible to make a tentative diagnosis during life, from the anemia with its characteristic blood changes; but an absolutely certain diagnosis must, of course, rest on the finding of the pathognomonic changes in the bone marrow as revealed by necropsy. Minot believes that the disease may bear some relation to purpura hemorrhagica. In both conditions there is a diminution in the number of platelets with the accompanying hemorrhagic tendency, but in many cases of aplastic anemia the anemia is marked before any severe hemorrhages have occurred, as in my own case; and in purpura hemorrhagica, the polymorphonuclear leukopenia is absent (Table 3). If the patient is under observation for any length of time it will usually not be difficult to differentiate the condition from an aleukemic phase of a lymphatic leukemia. The severe secondary anemias of the Von Jaksch type occur almost always in infants. They are associated with an enlarged spleen and an entirely different blood picture. The latter shows evidence of increased bone marrow activity.

The disease from which it is most important and difficult to differentiate aplastic anemia is pernicious anemia (Table 3). In fact, some authors still describe aplastic anemia as a form of pernicious anemia. However, the majority now recognize it as a distinct condition. Pernicious anemia is exceedingly rare in young children. In many of the reported cases the diagnosis is doubtful. Some years ago, Monti and Berggrün collected sixteen cases including one of their own. Of these only a few cases were verified by postmortem examination, including an examination of the marrow. In many of the remaining cases the clinical, including the blood, findings are very incomplete. Even in some of those cases in which the data are complete the diagnosis may be considered doubtful. For example, a case is reported by Escherich in which the symptoms were: anemia, general weakness, blood in the stools. Blood: hemoglobin, 10 per cent.; red blood cells, 575,000; white blood cells, 7,000 (on one examination, 3,500); marked reduction in polymorphonuclears. Slight changes in the form, size and color of the red blood cells, but no nucleated cells. A reduction in the platelets. A necropsy was not held.

The differential diagnostic points in these two diseases are given in Table 3, the chief being the difference in the color of the skin, the absence of urobilin in the urine, the blood picture with its absence of evidence of bone marrow activity, the absence of increase in the number of platelets following the injection of epinephrin, the positive constriction test, the increased bleeding time, the usually lower color index, and the diminished bilirubin content.

TABLE 3.—DIFFERENTIAL DIAGNOSIS BETWEEN PERNICIOUS ANEMIA, APLASTIC ANEMIA AND PURPURA HEMORRHAGICA (ESSENTIAL THROMBOPENIA—GORKE [11])

	Pernicious Anemia	Aplastic Anemia	Purpura Hemorrhagica
I. General Symptoms:			
Color of skin	Straw yellow	Alabaster white, cadaveric	Good, to extreme pallor
Hemorrhage of skin and mucous membrane	Unusual	Usually marked	In crops with free intervals
Mouth	Tongue smooth, edges atrophic; vesicles	Unchanged tongue; gingivitis; stomatitis; necrotic angina	Petechial hemorrhages; usually gingivitis
Spleen	Usually moderate enlargement	Not enlarged	May be enlarged
Urine	Urobilin present	Urobilin absent	Urobilin occasionally present
Secretion of gastric juice	Diminished	Occasionally diminished	Normal
Stools	Urobilin present	Very little urobilin	Normal
II. Blood:			
1. Morphology:			
(a) R. B. C.	Diminished number; anisocytosis; polychromatophilia; normoblasts; megaloblasts	Markedly diminished; no change in form; no nucleated red cells; no erythroblastic reaction	Variable; sometimes polycythemia; few young forms
(b) W. B. C.	Leukopenia; often relative lymphocytosis	Leukopenia; marked reduction of polymorphonuclears	Often leukocytosis; no change in differential count
(c) Platelets*	Diminished; epinephrin causes increase; splenectomy causes increase	Diminished; epinephrin and splenectomy cause no increase	In attacks marked thrombopenia; epinephrin and splenectomy increase
2. Constriction test†	No petechia	Hemorrhage, skin	Hemorrhage, skin
3. Bleeding time	Normal	Increased	Increased in attack
4. Retraction clot	Normal	Imperfect	Imperfect
5. Katalase index‡	Increased	Normal	Normal
6. Color index	Over 1	Ususally 1	Under 1
7. Fragility, coagulation time	Normal	Normal	Normal
8. Bilirubin content	Increased	Diminished	Normal

* The epinephrin test is made by injecting 1 mg. epinephrin, comparing the platelet count before and after the injection.

† The constriction test is made in the usual way by constricting the arm with a band and noting if hemorrhage results.

‡ The katalase index is normally between 6.1 and 6.8. It depends on the presence of a ferment which splits up hydrogen peroxid into water and oxygen.

The postmortem findings in these two diseases are distinct. In pernicious anemia there is a hyperplasia of the bone marrow; the production of new cells fails to keep up with destruction. In aplastic anemia there is an aplasia, or at least a hypoplasia, of the marrow. There is deficient production of new cells, but no evidence of increased destruction. In pernicious anemia there is a marked deposit of hemosiderin in the liver and the body fat is canary yellow; in aplastic anemia there is rarely a hemosiderin deposit, and the body fat is not canary yellow.

Prognosis.—In those severe cases in which the disease has come on suddenly, so that the time of onset is definitely known, the duration has been from one to three months. Mostly all authors consider the disease as being invariably fatal. This may be true for adults, but in children there appears to be a less acute form from which recovery is possible. Such a case is reported by Parkinson [5] and another by Benecke.[2] In my own case, the time elapsed is still too short to speak of a cure.[10] In Larrabee's case [11] there was a remission of several months. In the child we are dealing with a growing organism; the hemopoietic system is particularly active, so that if there is a marked hypoplasia rather than an aplasia, the possibility of regeneration is conceivable. In Parkinson's and Benecke's cases, and in my own case, the gradual but progressive improvement in the blood picture, together with the improvement in the appearance, temper and appetite would tend to show that regeneration is possible in the less acute, malignant form of the disease. The permanency of the improvement in the blood picture following transfusion is a good indicator of prognosis. It is interesting to note that in the secondary aplastic anemia following roentgen-ray exposure, and the injection of arsphenamin, although the characteristic changes are present in the blood, if roentgen-ray treatment or arsphenamin injections are discontinued, regeneration is possible and the patient may recover.

Treatment.—Preparations of iron, so valuable in other forms of anemia, are of little or no value in this form. A few patients have been somewhat benefited by injections of arsenic. Benecke's patient received "solarson," an arsenic preparation used at Klemperer's clinic, and recovered. Preparations of bone marrow have been given without any favorable effect. Radiation of the bone with the roentgen ray may be injurious rather than beneficial. The best method at our command at present is transfusion of whole blood. The investigations of Unger and others would seem to make it advisable to use the blood without the addition of sodium citrate. From 300 to 500 c.c. are usually given and repeated if necessary. In this way the platelets are at least temporarily increased and the hemorrhagic tendency is diminished. Fresh blood is supplied to the organism, and in some cases at least this seems to have also a stimulating effort on the bone marrow. If after a temporary improvement, the blood rapidly tends to return to its previous condition, the outlook is unfavorable; however, if a slight but progressive increase in the percentage of hemoglobin, in the number of red blood cells, in the polymorphonuclear leukocytes and in the platelets takes place, the prognosis is not unfavorable. In such cases there are probably still some small areas of normal marrow which may be reac-

10. The patient died at home April 25, 1922; no necropsy was obtained.
11. Larrabee: J. A. M. A. **75**:1632 (Dec. 11) 1920.

tivated so that the patient is tided over the danger period. Splenectomy has been performed in one or two cases with unfavorable result. It appears to be contraindicated.[12]

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12. Smith[7] gives a fairly complete bibliography up to 1918. The following may be added: Benjamin: Verhandl. d. Gesellsch. f. Kinderh., Karlsruhe, 1911. Frank: Berl. klin. Wchnschr. **37**:961, 1915. Helly: Prag. med. Wchnschr. No. 52, 1908. Irisawa and Koga: Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo **18**: 179, 1918. Symmers: Interstate M. J. **24**:1103, 1917. Westenrigk: Russk. Vrach. No. 36, 1912. Glenn and McVey: Northwest Med. **18**:65, 1919. Gorke: Deutsch. Arch. f. klin. Med. **136**:143, 1921. Jerosch: Med. Klin. **16**:1058, 1920. Musser: M. Clin. N. America **3**:1416, 1919. O'Malley and Conrad: J. A. M. A. **73**:1761 (Dec. 6) 1919. Von Willebrand: Finska läk.-sallsk. handl. **60**:859, 1918.

SPASMOPHILIA AND THE ALKALI RESERVE OF THE BLOOD*

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AND

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Wilson and his co-workers[1] pointed out that in parathyroidectomized dogs, just previous to the attacks of tetany, an increased alkalinity of the blood develops, a condition termed by them "alkalosis," which is neutralized by the acid products generated by the tetanic contractions of the musculature. Recently Grant and Goldman[2] have shown that forced respiration may cause symptoms of tetany to appear in the human. In these cases the underlying factor appears to be an "alkalosis." The forced breathing causes an excess of carbon dioxid to be exhaled from the lungs, thereby reducing the amount in the blood. This results in an increased alkalinity of the blood. However, they observed that the tetanic movements apparently produce acid products which tend to compensate for the increased alkalinity until a readjustment takes place.

Clinically it has at times been noted[3] that after the therapeutic administration of sodium bicarbonate for acidosis, characteristic symptoms of tetany may develop. These symptoms cease promptly when the sodium bicarbonate is stopped.

Howland and Marriott[3] have made determinations of the hydrogen ion concentration of the serum of infants with tetany by the dialysis indicator method, but have not found an "alkalosis."

Acute infections frequently precipitate active manifestations of spasmophilia in those having the latent form previous to the infections. As acute infections are usually accompanied by a tendency to acidosis, alkalosis could scarcely be a factor in producing tetany in this type of case.

Jones and Nye[4] found no relation between the alkali reserve and the concentration of calcium and phosphoric acid in the blood. Other investigators believe that the hydrogen ion concentration of

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1. Wilson, Stearns and Thurlow: J. Biol. Chem. **23**:89, 1915. Wilson, Stearns and Janney: ibid. **23**:123, 1915.
2. Grant, S. B., and Goldman, A.: Am. J. Physiol. **52**:209, 1920.
3. Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**:289, 1917.
4. Jones, M. R., and Nye, L. I.: J. Biol. Chem. **47**:331, 1921.

the serum (and the factors regulating this as the carbon dioxid tension and the alkali reserve) influence the type of calcium and phosphate salts formed, and consequently the relative amounts of calcium and phosphate ions available and the solubility of their salts.[5]

We determined the carbon dioxid combining power of the blood plasma by the Van Slyke method[6] in several cases of active spasmophilia in infants and again after their recovery.

REPORT OF CASES

The following are the histories, in abstract, of the patients we have studied:

CASE 1.—G. D., aged 15 months, colored, weight 14 pounds, was admitted to Cook County Children's Hospital, April 3 with evidence of an early bronchopneumonia and signs of active tetany consisting of marked laryngospasm, Chvostek, Trousseau and an Erb's electrical reaction of C.O.C. = 3.5 ma. There were also signs of marked rickets. The tetany cleared up on treatment with calcium bromid, and cod liver oil with phosphorus, and was reprecipitated by a course of sodium chlorid, 15 grains, and potassium citrate, 10 grains, given once daily. Six days after starting the sodium and potassium salts there was a definite Chvostek, a moderate Trousseau and a C.O.C. of 2.5 ma. Blood was drawn at this time from the longitudinal sinus to be examined by the Van Slyke method for a determination of the carbon dioxid combining power, and it was found that there were 40 c.c. of carbon dioxid bound as bicarbonate by 100 c.c. of plasma. The patient was again placed on calcium lactate, 3 grains, twice daily, and cod liver oil with phosphorus, 1 dram, three times daily, after stopping the sodium and potassium salts. At the end of six days of this treatment, the C.O.C. was 15 ma., there was no carpopedal spasm and only a very faint Chvostek. The blood reading showed 53.3 c.c. of carbon dioxid bound as bicarbonate by 100 c.c. of plasma. Eighteen days later there were still no clinical manifestations of spasmophilia and the blood reading was 46.2 c.c. of carbon dioxid.

CASE 2.—E. M., aged 3 years, colored, weight 17 pounds, was admitted May 23, 1921, suffering from pertussis, very marked rickets and active tetany consisting of marked laryngospasm, Chvostek and C.O.C. of 4 ma. with generalized convulsions. The next day the child was placed on 1 dram of phosphorized cod liver oil and calcium lactate, 5 grains, three times daily, and antispasmodics for the pertussis. The day that this treatment was instituted the blood reading was 42.4 c.c. of carbon dioxid, the spasmophilic signs were the same, although no convulsion had occurred during the previous eighteen hours. The C.O.C. was 3.5 ma. On examination twenty-two days later there were no signs of spasmophilia; C.O.C. 12 ma., and the blood[7] reading was 59 c.c. of carbon dioxid. Nine days later there were still no clinical manifestations of tetany, and the blood reading showed 55.3 c.c. of carbon dioxid combined as bicarbonate to 100 c.c. of plasma.

CASE 3.—M. M., twin of E. M., was admitted the same day and with the same clinical findings but no generalized convulsions. C.O.C. = 4 ma. The blood reading on admission was 47 c.c. of carbon dioxid. After having been on cod liver oil and calcium lactate for eleven days with no signs of tetany, the blood[7] reading was 50 c.c. of carbon dioxid.

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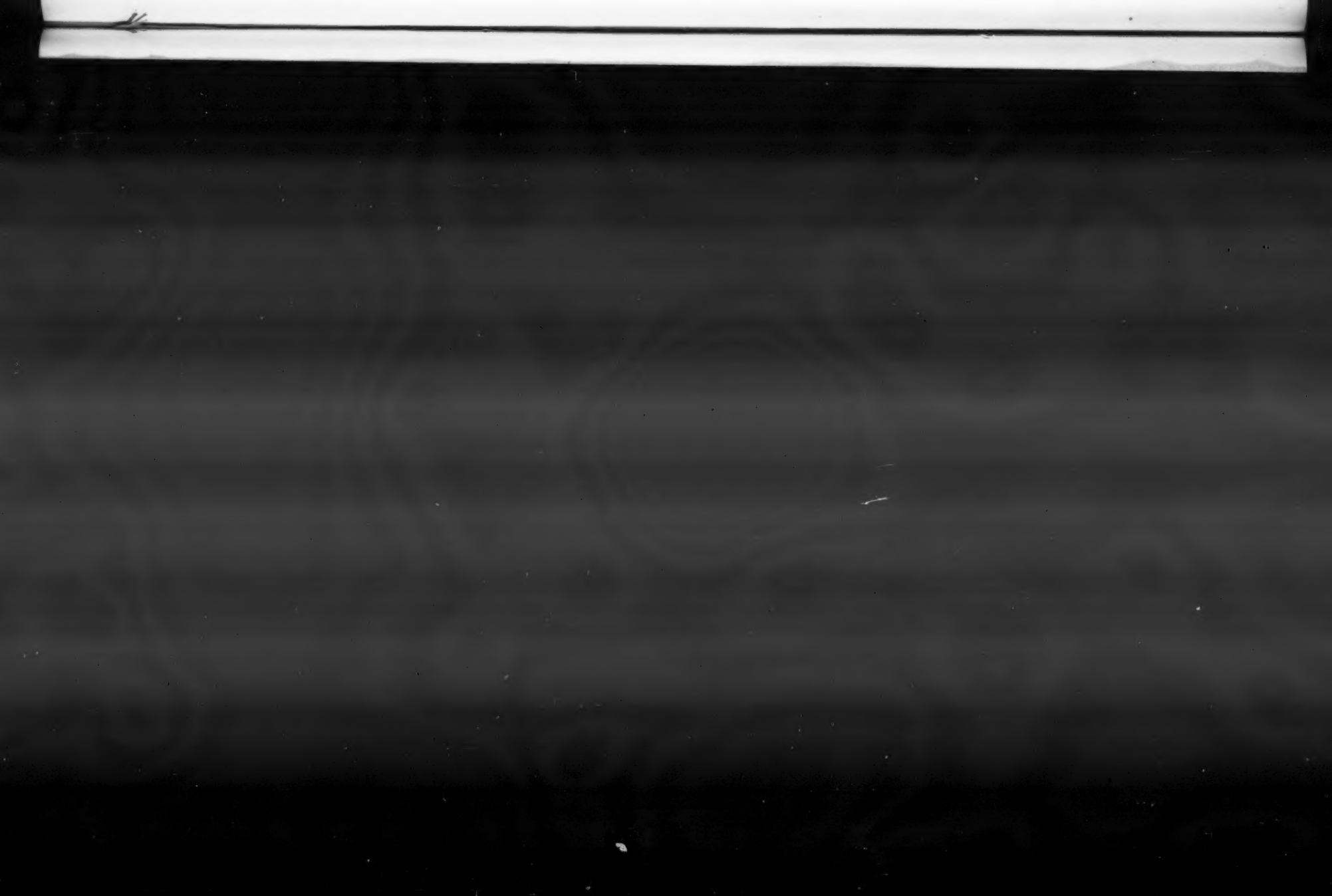
5. Howland, J., and Kramer, B.: Am. J. Dis. Child. **22**:105 (July) 1921.
6. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:317, 1917.
7. The blood was obtained from the external jugular vein.



CONCLUSIONS

In the cases of spasmophilia in the infants studied, no evidence of "alkalosis" was found. In fact, there was a tendency for the alkali reserve to be lowered during the spasmophilic stage and gradually to be increased as the cases recovered.

It appears that the symptoms of tetany may be produced in a variety of ways, but the evidence is not forthcoming that "alkalosis" plays a part in the genesis of infantile spasmophilia.

We wish to thank Dr. Welker and the Department of Physiological Chemistry of the University of Illinois for the privilege of using their laboratories for the blood chemistry work.

ACTIVE IMMUNIZATION OF NURSES AGAINST DIPHTHERIA IN A CHILDREN'S HOSPITAL*

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ST. LOUIS

The immunization of children against diphtheria by toxin-antitoxin mixtures has been carried out on a considerable scale with excellent results. Two of the more recent series in which the immunity was confirmed by later Schick tests are those reported by Zingher [1] and by Blum.[2] Such immunization has been advised for susceptible physicians and nurses, especially those caring for children, since they are more intimately exposed to diphtheritic infection. No studies on groups of adults, however, have been reported. Herewith are presented the results of a systematic immunization of all the susceptible individuals in a nurses' training school over a period of years. All the individuals were on duty in the Contagious Pavilion of the St. Louis Children's Hospital during a part of their training, usually from one to two months, and the incidence of diphtheria in the group before and after the immunization was instituted has been noted.

METHODS

The toxin for Schick tests and the toxin-antitoxin mixture used were obtained through the New York City Board of Health. Beginning in 1918, Schick tests were performed on all pupil nurses of the Washington University Training School, except those who had completed their service on the contagious wards. Subsequent entrants were tested when admitted. The nurses reported in groups of from six to fifteen so that any given group furnished both positive and negative reactions. In every case a control of the same amount of toxin heated to 75 C. for five minutes was also done. Readings were made at the end of two and four days and a final observation was made on the sixth or seventh day. Any definite reaction at that time was considered positive. A strongly positive reaction was designated + +, one of moderate intensity + and a faint positive reaction ±. All nurses who gave positive reactions were immunized by three subcutaneous injections of toxin-antitoxin mixture (3 L + doses + 3½ units), given at intervals of one week, and the Schick test was repeated four months later.

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* Received for publication, March 9, 1922.

* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Zingher, A.: Active Immunization of Infants Against Diphtheria, Am. J. Dis. Child. **16**:83 (Aug.) 1918.

2. Blum, J.: Active Immunization Against Diphtheria in a Large Child-Caring Institution, Am. J. Dis. Child. **20**:22 (July) 1920.

Before giving the results of the study, brief mention may be made of certain general observations concerning the tests. Pseudoreactions were noted in 38 per cent. of sixty-one negative Schick tests, but in these are not included some slight reactions of about 1×1 cm. consisting of a faint erythematous blush which persisted for two or three days. The largest pseudoreaction measured 8×13 cm. with the central deeper red area 2×2 cm. in size. Some of the more intense pseudoreactions did not fade completely even at the end of a week and a faint brownish pigmentation remained. Combined reactions were shown in about 20 per cent. of the positive tests. Since readings were made at intervals on all the tests, there was opportunity to observe whether the reading on the second day differed from that on the later examinations. In nineteen instances out of 222 there were well marked changes in the test, some fading while others became more intense. Ten tests which were + or ± on the second day became more marked at the end of four days, while three cases which were — became +; in four instances a + reaction became ±, and two ± reactions had faded completely in four days and were read —. These changes were quite independent of any pseudoreactions in the controls.

The reactions following the injections of toxin-antitoxin, as a rule, were somewhat similar to those following prophylactic typhoid vaccination. Usually there was a well marked local redness, swelling and tenderness of an area several cubic centimeters in diameter persisting for from twenty-four to forty-eight hours. Many remembered some listlessness and headache when questioned a week later. In only two individuals was the effect at all severe. A marked general reaction with a chill and temperature of 103 F. followed the injection, with general malaise and headache continuing from three to four days. The arm was greatly swollen from elbow to shoulder with a large area of red and purplish discoloration at the site of injection, accompanied by marked tenderness and disability. A similar reaction followed each injection.

In all, Schick tests were performed on 147 nurses of whom sixty-one, or 41.5 per cent., gave negative reactions and eighty-six, or 58.5 per cent., gave positive reactions. Of the latter, thirty-nine were + +, thirty-seven were + and ten were ±. This high percentage of positive reactions was unexpected and differs considerably from the figures usually given for adults (about 30 per cent.). The relative proportion of positive and negative reactions was remarkably constant, however, in the separate groups tested and did not vary in the different years.

One possible explanation for the high incidence of susceptible individuals in this group of nurses is that the majority of them were reared in small communities where diphtheria is far less prevalent than in cities. There is considerable evidence that contact with diphtheria

cases plays an important part in the development of an antitoxic immunity. The morbidity statistics in Pennsylvania,[3] for example, during the years 1916-1918 show that diphtheria was much more prevalent in urban than in rural communities, the relative proportion being 530 in the urban to 370 in the rural. The figures quoted by Zingher,[4] from the examination of school children show conclusively that children from congested districts in cities show a much higher percentage of immunes than those from more sparsely settled sections and rural communities. The percentage of positive Schick tests usually given for adults is considerably lower than that found in children, and it seems quite probable that this increased immunity in later life depends, at least in part, on contact with diphtheria organisms since the antitoxin is a specific antibody. In the larger cities diphtheria is endemic, and each year there is a large morbidity. In St. Louis, for example, the morbidity is about 0.5 per cent. of the population per year. It seems certain that many cases of slight unrecognized infection also occur, and it is probable that, as in other communicable diseases, these mild and missed cases contribute to the spread of the infection. In cities, therefore, it might be expected that many adults would have an acquired immunity and that the number of immune adults would be proportionally more than in childhood. The figures of Park[5] in New York (33 per cent.), Kolmer[6] in Philadelphia (35 per cent.), Bundesen[7] in Chicago (33 per cent.), Moody[8] in St. Louis (27 per cent.), and Leete[9] in Edinburgh (34 per cent.) indicate that such is the case. In smaller communities, such as villages, towns and even the smaller cities, on the other hand, diphtheria is not prevalent, and many such communities are free from the disease for long periods, although the occasional epidemics which occur show a higher mortality than in cities. Extensive statistical studies on diphtheria immunity, as shown by the Schick test in these smaller communities, are not available, but it is significant that Lilly[10] found 57.6 per cent. of positive reactions

3. Hull, H.: Diphtheria from the Public Health Standpoint, Penn. M. J. **23**:638 (Aug.) 1920.

4. Zingher, A.: Diphtheria Preventive Work in the Public Schools of New York City, Arch. Pediat. **38**:336 (June) 1921.

5. Park, W. H.; Zingher, A., and Serota, M. H.: The Schick Reaction and Its Practical Applications, Arch. Pediat. **31**:481 (July) 1914.

6. Kolmer, J. A., and Moshage, E. L.: The Schick Reaction for Immunity in Diphtheria, Am. J. Dis. Child. **9**:189 (March) 1915.

7. Bundesen, H. N.: Schick Reaction with a Report of 800 Tests, J. A. M. A. **64**:1203 (April 10) 1915.

8. Moody, E. E.: The Intradermic Diphtheria Toxin Test, J. A. M. A. **64**: 1206 (April 10) 1915.

9. Leete, H. M.: The Schick Reaction, Lancet **1**:192 (Jan. 24) 1920.

10. Lilly, T. E.: An Experience with the Schick Test and Toxin-Antitoxin, and a Plea for Their Use in the Extinction of Diphtheria, Boston M. & S. J. **182**:110 (Jan. 29) 1920.

in 257 boys from 15 to 21 years old in the Industrial Home for Boys at Shirley, Mass. Tests made on a number of students in the Washington University Medical School, two-thirds of whom come from smaller towns, show a similar high percentage of positive Schick reactions. More recently Garland [11] has found that of 380 nurses tested in a number of Massachusetts hospitals 52.8 per cent. gave positive Schick reactions.

The effect of the toxin-antitoxin injections on the Schick reaction is shown in Tables 1 and 2. Not all the nurses who gave positive reactions are included since some left training, and a group of army nurses were not immunized because they did not have duty on the diphtheria

TABLE 1.—EFFECT OF FIRST SERIES OF TOXIN-ANTITOXIN INJECTIONS ON SIXTY-TWO NURSES WITH POSITIVE SCHICK REACTIONS

	62								
Before toxin-antitoxin	27++			27+			8±		
4 months later	1++	6+	1±	19—	4+	1±	22—	2±	6—
From 9 to 15 months later	1++	4+	2—	1±	2+	2*	1±	1±	1*

* Not retested.

TABLE 2.—EFFECT OF A SECOND SERIES OF TOXIN-ANTITOXIN INJECTIONS ON EIGHT NURSES WHO WERE NOT IMMUNIZED BY THE FIRST SERIES

	8					
Before second series.....	1++		4+		3±	
From 4 to 8 months later	1—	2+	1±	1—	2±	1—

wards. In all sixty-two nurses have been given the toxin-antitoxin, and when retested from four to six months later, forty-seven, or 75.8 per cent., were immune. Two more gave negative reactions nine and fifteen months after the injections, bringing the total number immunized to 79 per cent. Of the remaining thirteen, five had graduated or had left training before further tests could be performed, but the remaining eight were given a second series of three toxin-antitoxin injections (Table 2). Only three of these gave negative reactions when

11. Garland, J.: Report on the Recent "Schick Test" Campaign, Boston M. & S. J. **185**:432 (Oct. 13) 1921.

tested later. Since in a certain number of instances the immunity is late in developing it is not certain whether these three negative reactions resulted from the first series of injections or from the second. Certainly a few individuals appear definitely refractive to immunization as indicated by the Schick test.

The effect of the immunization on the incidence of clinical diphtheria in the group of nurses studied is especially striking and is shown in Table 3.

It will be noted that twenty nurses, or 28.6 per cent. of those on duty in the contagious pavilion, developed diphtheria during the three years preceding the immunization, while only two in the group (1.5 per cent.) contracted the disease in a four years' period after the immunization was started. One of the latter was assigned to duty on the diphtheria ward through an error just after her first dose of toxin-antitoxin,

TABLE 3.—EFFECT OF IMMUNIZATION ON DIPHTHERIA MORBIDITY IN NURSES

	Before Immunization of Nurses			After Immunization of Nurses			
	1915	1916	1917	1918	1919	1920	1921
Cases of diphtheria reported in St. Louis	3,389	3,114	3,339	2,015	3,976	4,660	3,561
Cases of diphtheria and diphtheria carriers treated in the St. Louis Children's Hospital	110	69	87	70	126	110	132
Total nurses in Washington University Training School	73	85	92	110	80	99	106
Washington University nurses on contagious service	20	32	18	32	35	31	32
Washington University nurses with diphtheria	7	9	4	0	1*	1†	0
Total affiliated nurses (not immunized)	24	20	24	25	14	19	31
Affiliated nurses with diphtheria (not immunized)	2	1	0	2	0	1	4

* Nonimmune on duty in diphtheria ward by mistake.
† Diagnosis uncertain.

and two days later developed clinical diphtheria. In the other instance, a nurse who had been immunized and had a negative Schick reaction one year previously, developed a slightly red throat which was painted with a strong silver nitrate solution. Cultures taken were positive for diphtheria bacilli and a grayish exudate developed on both tonsils. It was thought wiser to administer antitoxin and she recovered promptly. Cultures remained positive for more than a month. It could not be decided definitely whether the exudate was diphtheritic or the result of the superficial necrosis from the silver nitrate application in a nurse who was a diphtheria carrier. A Schick test done six months after the illness was negative, so that the latter assumption is probable.

More cases of diphtheria were treated in the wards during the period after immunization than during the previous three years, and the morbidity in the city was also slightly higher during this latter period. As controls may be taken the group of nurses from several affiliated

institutions who spent three months in the Children's Hospital, part of the time in the contagious pavilion. No skin tests or immunity studies were made on this group. Their contact with patients was the same as that of the nurses of the Washington University Training School except that they spent only about half the time on duty in the contagious disease wards. In each of the three-year periods, 1915-1917 and 1918-1920, three nurses from this group contracted diphtheria and four more during 1921. It might be mentioned, also, that during the latter period in which the Training School Nurses were immunized, two interns and four of the maids and office help in the Children's Hospital developed clinical diphtheria.

The effect of immunization by toxin-antitoxin on this group of adults was of particular interest on account of the fact that all were exposed to diphtheria during their training. That a considerable proportion was susceptible to the infection is shown by the rather high morbidity in the group during the control period of three years before immunization was instituted. During this time 28.5 per cent. of the nurses in the contagious pavilion developed clinical diphtheria. This must be regarded as a minimum since probably all were not exposed to the infection equally. For example, certain nurses were probably detailed to scarlet fever, or measles wards for a considerable portion of their service and may have spent only a few days on the diphtheria ward. The actual intimate exposure to diphtheria cases, therefore, varied with the number of cases of other communicable disease which happened to be treated in the hospital. The number of susceptible individuals during the first three years' period as indicated by those having clinical diphtheria is consequently not absolutely comparable to the susceptibles of the second four years' period as indicated by the Schick test. However the individual exposure may have varied during the two periods, the group exposure during these periods can be compared and it will be noted that almost double the number of patients with diphtheria were cared for by the immunized group than by the control group. The almost perfect protection from infection by the immunization is, therefore, more striking.

The number of individuals in whom the Schick reaction remained positive after three doses of toxin-antitoxin is somewhat larger than is usually reported in children after immunization. Even after a second series of injections five out of a group of eight were persistently positive. All these nurses have completed their service in the contagious pavilion and none has developed diphtheria. In such a small number no conclusion regarding immunity is possible. It would seem that if a negative Schick reaction does not follow three injections of toxin-antitoxin, further injections are also likely to fail in suppressing the reaction.

SUMMARY

The Schick test was positive in a group of adults (nurses) in 58.5 per cent. It is suggested that this high proportion of nonimmunes may be related to the fact that most of the individuals in the group were reared in smaller communities where contact with diphtheria is less than in cities.

During a four years' period all nurses with positive Schick reactions were given injections of toxin-antitoxin, and as a result more than 80 per cent. were immunized. In a small number the Schick reaction remained positive after two series of toxin-antitoxin injections.

As a result of the immunization, there was a decrease in the incidence of clinical diphtheria among these nurses of at least 90 per cent. as compared to a previous three years' period.

It is relatively easy to protect an entire nursing staff from contracting diphtheria by the use of the Schick test and toxin-antitoxin injections, and this procedure should be carried out in all institutions caring for children.

I wish to thank the staff of the Washington University School of Nursing for assisting in this study, and especially Miss Minnola Stallings, whose interest and cooperation have greatly facilitated the work.

THE ASPIRATION OF STEARATE OF ZINC IN INFANCY

A CLINICAL AND EXPERIMENTAL STUDY *

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NEW YORK CITY

During the past few years stearate of zinc has largely replaced talcum as a dusting powder in the nursery. With its ever widening use there has developed a striking increase in the number of disastrous results in infants from its accidental aspiration.

We thought it might be worth while to present a clinical study of twelve cases observed by one of us (Heiman) and the results of experiments with zinc stearate insufflation in animals (Aschner). The cases were observed in private practice and in the Children's Wards of Mt. Sinai Hospital.

To understand the mode of aspiration one must be familiar with the powder as prepared for use in the nursery. It is packed in a cylindrical box having large perforations at one end in order to "shake out" the powder. Usually a sliding cover is provided. The perforations are made unusually large because of the tenacious quality of zinc stearate. The infant takes hold of the box, as it does its nursing bottle, and draws it quickly toward the face. If the sliding cover has been left open, there is a sudden shower of a large mass of powder, which partially or wholly asphyxiates the infant. Some of the powder is thus aspirated into the bronchi and lungs.

The onset of trouble is sudden and stormy, with rapid respirations and cyanosis. Complete asphyxia may occur. One of our patients died within twenty-four hours after the accident. The infant, aged 8 months, was given a box of zinc stearate to play with. The powder spilled on the child's face producing an asphyxia with marked dyspnea and cyanosis. At the hospital the Auer-Meltzer apparatus, as well as hypodermic stimulation were employed without avail. Physical examination of the lungs revealed the diffuse fine crepitating râles of an extensive bronchopneumonia. Postmortem examination (macroscopically) showed small areas of consolidation on the posterior aspect of both lungs.

All of the cases, however, are not of this fulminating type. Three infants developed signs of bronchopneumonia with symptoms of an

* Received for publication Jan. 9, 1922.

* From the Pediatric Service and the Pathological Laboratory of Mt. Sinai Hospital.

acute toxemia, which lasted from two to three weeks. The temperature was intermittent, varying from 99 to 105 F. Respirations were rapid in all these cases, in one case 90 per minute. Cyanosis was marked at the onset. The pulse was rapid. Abdominal distension was marked in two cases. Recovery was gradual by lysis during the third week. The treatment is that of bronchopneumonia. Hygienic care and efficient nursing are of prime importance. An abundance of fresh air

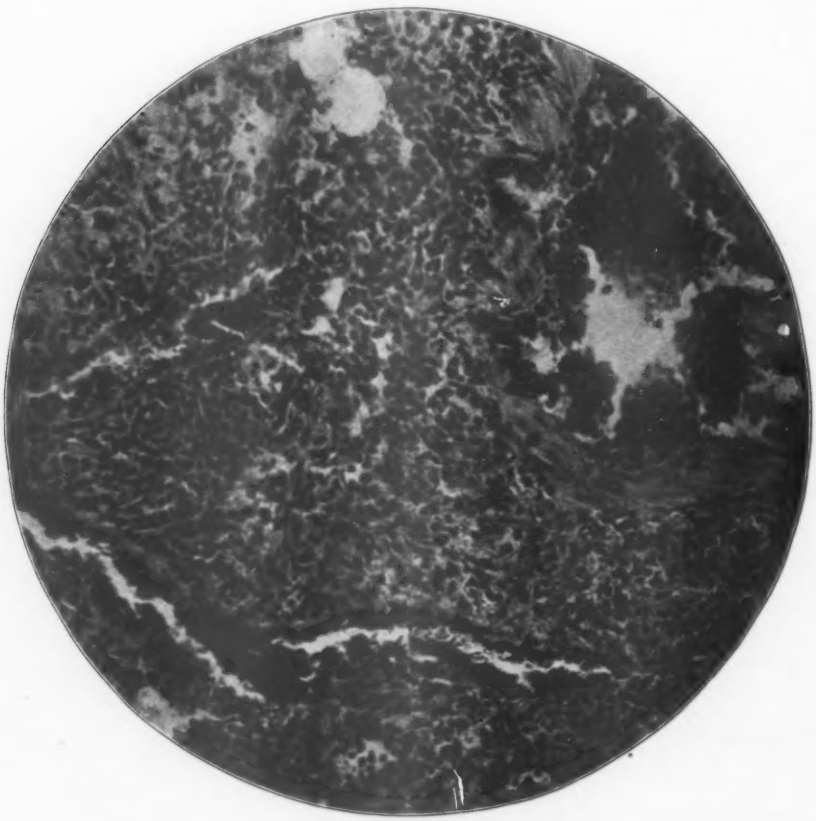

Fig. 1.—Proliferation of bronchial epithelium. Bronchopneumonia. X260.

and sunlight are essential. Diluted milk, gruels, fruit juices and water should form the chief elements of food. To provide proper elimination magma magnesiae in the morning and an enema should be given each night. Hydrotherapy in the form of warm packs between 80 and 90 F. and stimulation may be necessary.

In eight of our cases the initial partial asphyxia was followed by a gradual recovery without definite involvement of the lungs. The rapid respirations and cyanosis which followed immediately on the

inhalation of the powder subsided during the course of three days. The temperature was only slightly elevated.

The stearate of zinc container as now prepared for the nursery is a distinct menace to the health of infants. May we not enlist the efforts of the medical profession to eliminate this dangerous type of container from the nursery?

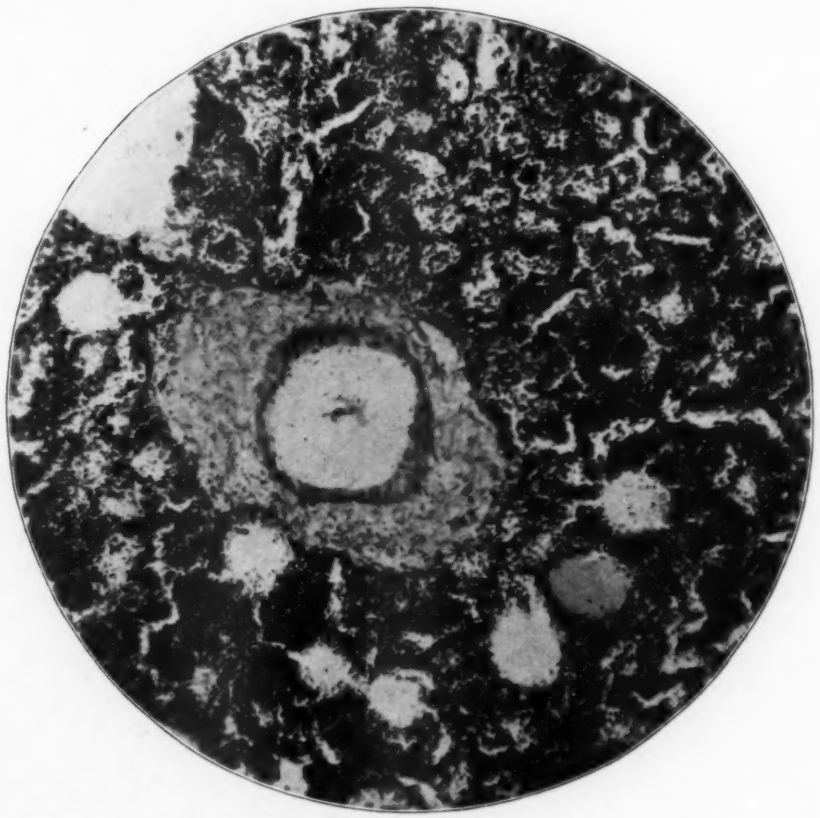

Fig. 2.—Hemorrhagic area. Perivascular edema. X170.

NECROPSY REPORT

The patient was 8 months old. There were no evidences of pleuritis. The lungs were salmon pink in color, air containing, with no extensive consolidation. Along the posterior borders were a few darker firmer areas. Microscopic sections showed intense congestion with areas of interstitial round cell infiltration. The bronchioles showed round and polymorphonuclear leukocytic infiltration of their walls.

Efforts to induce dogs to inhale zinc stearate in a manner similar to that which occurred in the clinical cases were unsuccessful. The

method used by Lamar and Meltzer [1] in their experimental production of pneumonia was therefore resorted to with slight modification. The animal was etherized. A sterile rubber tube, 1 cm. in diameter, was passed just beyond the vocal cords. Sterile zinc stearate was then insufflated through the tube with a DeVilbis powder blower. Samples of the powder from our cases had proved sterile with only one exception in which a gram-positive saprophytic bacillus was found.

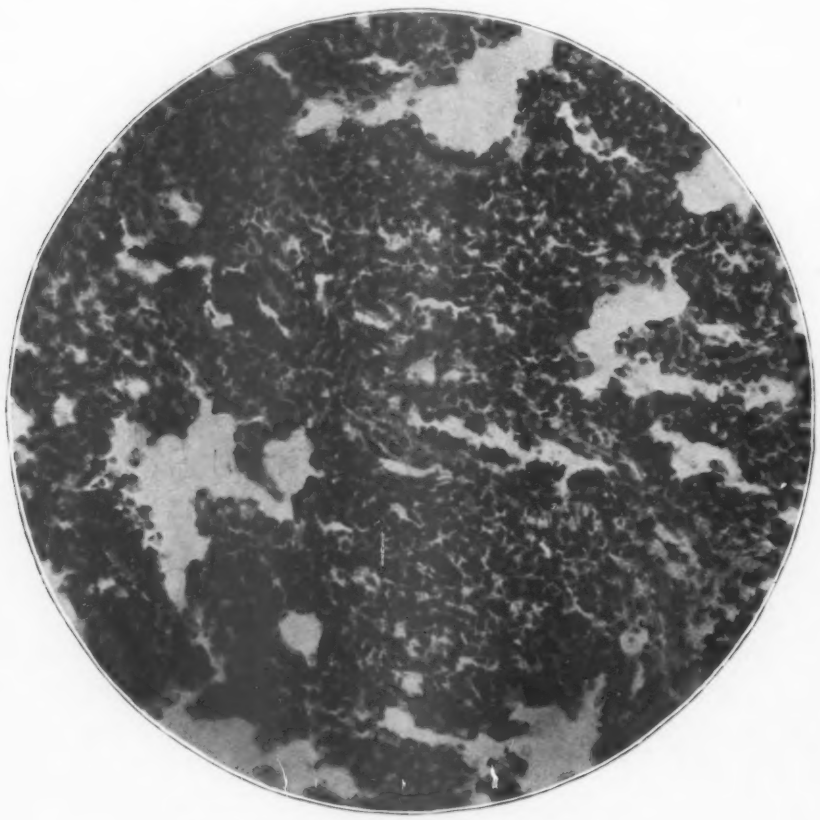

Fig. 3.—Interstitial pneumonitis. X260.

The bulb was squeezed four or five times, the tube was pinched a few seconds, and then withdrawn. Anesthesia was maintained for another five minutes.

The dogs appeared ill for a few days with loss of appetite and temperature of 101 to 103 F. Some dogs developed a dry brassy cough. Difficulty in breathing was of short duration. A few dogs

1. Lamar, R. V., and Meltzer, S. J.: J. Exper. M. **15**:133, 1912. Wollstein, M., and Meltzer, S. J.: J. Exper. M. **16**:126, 1912; **17**:353, 1913; **18**:543, 548, 1913.

showed practically no symptoms. Three dogs were killed three days after insufflation, two dogs after five days, and one dog ten days after. One dog was insufflated twice, another four times. The lesions produced can best be described by the following protocols.

Experiment 1.—Dog killed three days after zinc stearate insufflation. Lungs well aerated, very pink. Some small raised whitish areas in lower and middle lobes. Microscopic sections show congestion and increase of interstitial

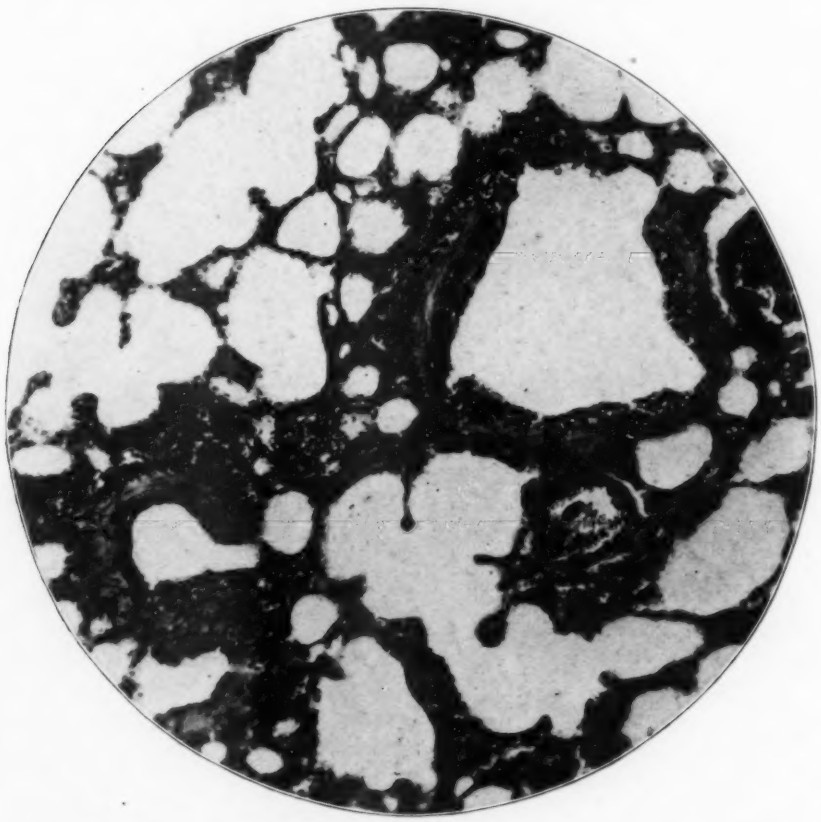

Fig. 4.—Slight interstitial pneumonitis after talcum insufflation. X170.

tissue especially in vicinity of the bronchioles. Vessels show perivascular edema, and in places round cell infiltration of their walls. Bronchioles show epithelial proliferation with some formation of polypoid excrescences. The lumen of some bronchioles contains amorphous detritus and round cells. The outer coats present round and polymorphonuclear cell infiltration with deposit of pigment. Parenchyma about bronchioles shows areas of alveolar desquamation with pigment in many of the desquamated cells. The picture is that of a catarrhal or bronchopneumonia (Fig. 1).

Experiment 2.—Dog killed three days after zinc stearate insufflation. Microscopic sections show interstitial pneumonitis and peribronchitis. There

are also areas of intense congestion and hemorrhage. Some of the vessels show edema, some contain thrombi (Fig. 2).

Experiment 3.—Dog killed five days after zinc stearate insufflation. Lungs very pink. The right lower lobe appears poorly aerated and feels heavy. Sections show widespread interstitial pneumonitis. Alveoli are reduced in size by a highly vascular connective tissue interstitium. The vestibulae appear numerous and prominent. Larger air passages show areas of submucous round cell infiltration (Fig. 3).

Similar lesions were obtained in all the experiments.

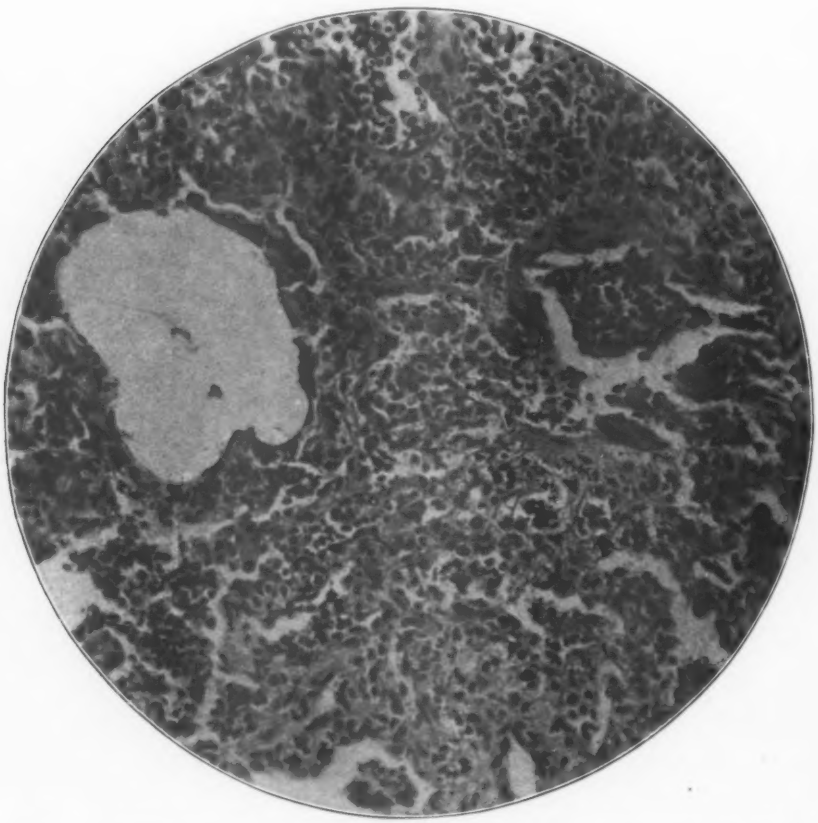

Fig. 5.—Area of more recent polymorphonuclear cell infiltration of parenchyma. X260.

For purposes of comparison two dogs were insufflated with sterile talcum powder with the following results:

Experiment 4.—Dog killed three days after talcum insufflation. No gross changes. Sections show few small scattered areas of peribronchial infiltration with round cells. No intrabronchial exudation, no changes in bronchial or alveolar membranes.

Experiment 5.—Dog killed five days after talcum insufflation. No gross changes. Sections show a rather diffuse but slight increase of interstitial

tissue with small round cell foci. There are round cell foci in walls of some larger bronchi and about the larger vessels (Fig. 4).

The lesions produced by talcum powder are similar in kind but lesser in degree than those produced by zinc stearate. It is probable that the physical properties of the talcum permit the animal to expel a good deal of the foreign material. Zinc stearate is, on the contrary, an extremely tenacious powder.

Fig. 6.—Area of older organizing pneumonitis. X260.

Cultures of the lung tissue were made in three instances and proved sterile in each.

It is of interest to note that Meltzer and Kline [2] insufflated unorganized substances and produced pneumonic lesions. Aleuronat and starch produced lesions similar to those obtained after insufflation of virulent pneumococcoi. Egg yolk and lecithin produced lesions resem-

2. Meltzer, S. J., and Kline, B. S.: Proc. Soc. Exper. Biol. & Med. **13**:29, 1915.

bling those of avirulent pneumococci and *B. megatherium*. Lung cultures in these experiments proved sterile.

Repeated insufflation of zinc stearate at intervals of about a week were carried out in one experiment.

Experiment 6.—Dog killed two days after last of four insufflations. Lungs white with some gelatinous areas along free margins. Bronchioles, some occluded by a hyaline material containing epithelial and round cells, peribronchial infiltration with round and polymorphonuclear cells. Adjoining areas of interstitial pneumonitis and alveolar desquamation. An extensive organizing fibrotic process is seen in the parenchyma (Figs. 5 and 6).

The production of a fibrosis of the parenchyma by repeated insufflation of zinc stearate may explain the beneficial results noted by Lynah [3] in cases of bronchiectasis and lung abscess after injections of bismuth mixtures by means of the bronchoscope. The bismuth is retained in the tissues for days after the procedure and probably induces an organizing process in the lung about the site of injection.

The authors wish to acknowledge their indebtedness to Dr. Jerome Ziegler for valuable aid in the animal experiments and to Dr. F. S. Mandlebaum, director of laboratories, for the microphotographs.

3. Lynah, H. L., and Stewart, W. H.: Ann. Surg. **73**:362, 1921.

HEALING OF HYPERTROPHIC PYLORIC STENOSIS AFTER THE FREDET-RAMMSTEDT OPERATION *

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NEW YORK

The following study is based on the gross and microscopic examination of the stomachs of twenty-five infants who came to necropsy with hypertrophic pyloric stenosis. Two children of the series died before operation, and the rest succumbed from twenty-four hours to two years after the Fredet-Rammstedt operation had been performed. The age of these children, at necropsy, ranged from 4 weeks to 2 years.

PATHOLOGY

The stomachs with hypertrophied pylorus, when observed before or soon after operation, were dilated and often twice the size of the normal stomach of the same age. The pylorus measured from 1.5 to 3 cm. in length as compared with the normal length of from 1 to 1.5 cm.. The feel of the pylorus was abnormally thick and hard.

On opening the stomach it was usually empty of food, but it always contained a large amount of mucus, with a thick plug in the pyloric opening. The mucosa showed nothing abnormal. The thickening of the pylorus was due to an increase in the width of the circular muscle coat, the other layers showing no change from the normal. In a few cases the wall at the pyloric end of the stomach was slightly thicker than usual, but at the cardiac end it was always normal. The measurements of the circular muscle coat of the hypertrophied pylorus compared with those of the normal pylorus in infants from 1 to 3 months old are given in the accompanying table.

It will be seen that in the hypertrophied pylorus the circular muscle was from 3 to 7 mm. thick, thirteen out of twenty cases measuring 4 mm. or more. The normal stomachs, on the other hand, showed a pyloric circular coat between 0.5 and 2.5 mm. in thickness, and seventeen measured 2 mm. or less. The contrast is marked. The normal thickness of the pyloric circular muscle coat in children under 3 months of age may be given as not greater than 2.5 mm., the average being 1.6 mm. The hypertrophic pylorus at this age, on the other hand, shows a circular muscle layer of from 3 to 7 mm. in thickness, the average being 4.4 mm.

MICROSCOPIC ANATOMY

On microscopic examination it was found that the changes were limited to the submucosa and the circular muscle coat. The mucosa

* Received for publication, Jan. 21, 1922.

* From the Laboratory of the Babies' Hospital.

was practically unchanged in every instance. The absence of any evidence of inflammatory lesion from this coat would seem to place the vomiting entirely in the mechanical category, due to over distension of the stomach because of the tightly closed pylorus. The submucosa was often edematous and thus apparently wider than usual. The characteristic change was seen in the circular muscle coat, which was at least twice and often three times thicker than normal. The thickness was due simply to a larger amount of muscle tissue in the circular coat, while the connective tissue between the muscle cells was not increased. In no case of my series had there been any fibrous con-

THICKNESS OF CIRCULAR MUSCLE COAT OF PYLORUS

Age Weeks	Normal Pylorus Mm.	Hypertrophic Pyloric Stenosis Mm.
4½	0.0025, 0.0005	0.0035
5	0.0021, 0.0015, 0.002	0.005, 0.006, 0.004, 0.007, 0.004
6	0.001, 0.0015, 0.0015	0.0035, 0.0035, 0.004
7	0.001, 0.00125	0.005, 0.0035
8	0.002, 0.00125	0.005, 0.003, 0.004
9	0.001, 0.002,	0.0045, 0.004,
10	0.001, 0.002	0.0045
10	0.002, 0.0015	0.0045, 0.0035
12	0.001, 0.0025	0.006,

nective tissue thickening. This fact was well demonstrated by staining the sections for connective tissue with Van Gieson's stain (Figs. 1 and 2). The hardness and firmness apparent on palpating the pylorus is due only to the thick and firmly contracted muscular ring. The serosa was normal when the specimen had been obtained before operation or after the healing of the operation wound. Edema was not present at either of these periods.

HEALING

The healing after the Fredet-Rammstedt operation, which consists simply in incising the serous and muscle coats of the pylorus down to the submucosa, is an interesting process, best illustrated by pictures of sections made from the stomachs at various periods after operation. My series includes sections from cases in which death occurred in twenty-four hours, four days, nine days, ten days, thirteen days, twenty-five days, six weeks, sixteen months and two years after operation. In twenty-four hours intense congestion of the blood vessels of all the coats along the line of incision, some edema of all the coats and hemorrhage into the submucosa were present. There was a wide gap between the cut ends of the muscle coats, over which lay a delicate layer of fibrin with few polymorphonuclear cells. The submucosa showed a similar cellular infiltration, more marked in some cases than in others.

In four days (Fig. 3), there was a small plug of fibrin in the base of the gap between the incised edges of the wound, and the connective

tissue of the serous coat had almost covered the cut ends of the muscle by proliferation of its cells, between which thin walled blood vessels were seen. The most superficial connective tissue cells had become flattened into a protective layer like endothelium over this delicate granulation tissue. Since we know that unstriped muscle cells regenerate only to a minimum degree, if at all, it remains for the connective

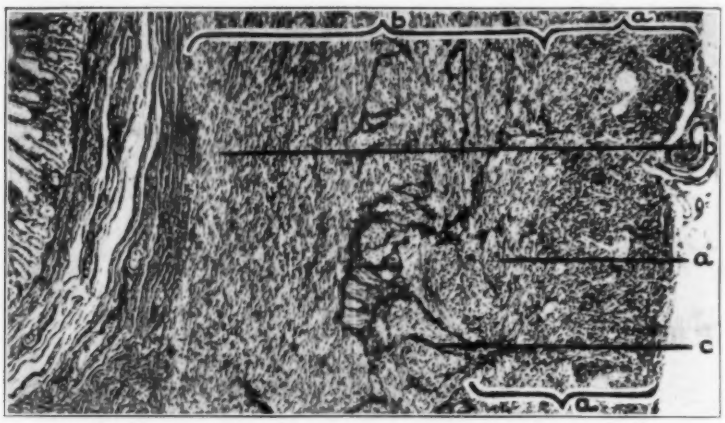

Fig. 1.—Normal pylorus: (a) longitudinal muscle coat; (b) circular muscle coat; (c) fibrous connective tissue.

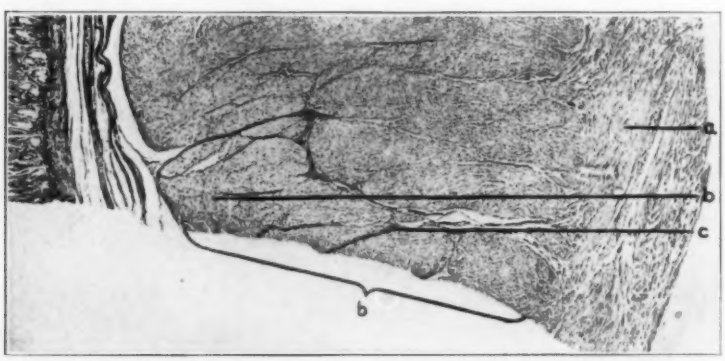

Fig. 2.—Hypertrophied pylorus: (a) longitudinal muscle; (b) circular muscle coat; (c) fibrous connective tissue. Note hypertrophied circular muscle and no increase in connective tissue.

tissue of the serosa and submocosa to fill in the gap between the edges of the operation wound. This proceeds as indicated above, and the muscle cells show no attempt at proliferation.

In nine days and ten days after operation (Fig. 4) the gap between the edges of the wound is still wide but the entire length of the incision

is covered with a delicate layer of cellular, fibrous connective tissue, which represents the proliferated serous coat, and touches the submucosa at the base of the incision. The cut ends of the muscle layers are still wide apart, and consequently there is a depression on the outer surface of the pylorus at the site of operation. At this time, however,

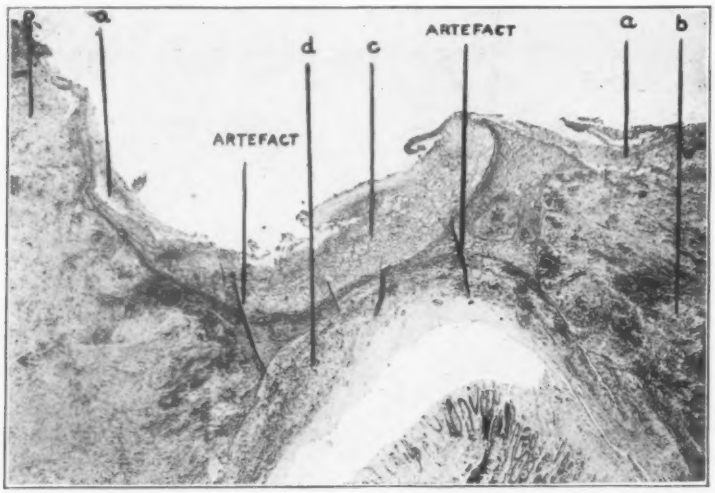

Fig. 3.—Four days after Fredet-Rammstedt operation. (a) Layer of delicate granulation tissue over edges of incised muscle (b) and in base of wound (c) close to submucosa (d) which shows cellular infiltration.

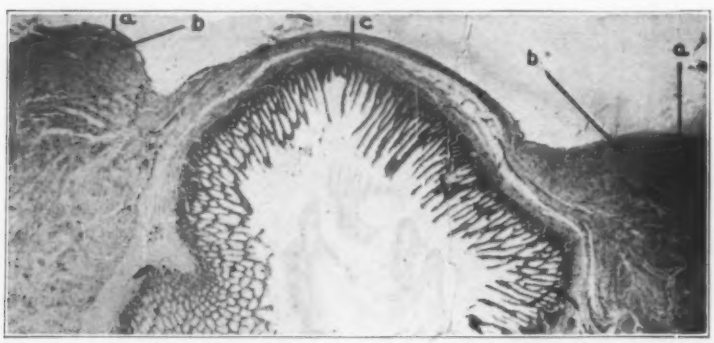

Fig. 4.—Ten days after operation. Wound healed. (a) Edges covered by thin layer of connective tissue. (b) Wide gap between cut ends of muscle coat. (c) Submucosa and serosa in contact.

as Dr. Downes has pointed out, the pylorus feels softer than at the time of operation.

As the muscle coat relaxes from gradual lack of obstruction and consequent cessation of overstimulation of its contractile power, and

the newly formed connective tissue, thin as it is, contracts, as all connective tissue tends to do, the two divided ends of the muscle coats tend to approach each other and the space between them becomes less and less. Twenty-five days after operation there is only a narrow scar at the site of the incision in the pylorus, and no longer a depression at this point. Microscopically there is a thin layer of fibrous connective

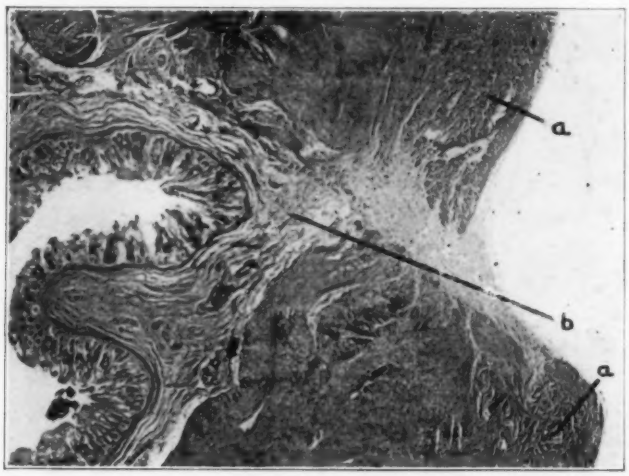

Fig. 5.—Twenty-six days after operation. (a) Ends of muscle coat drawn close together and layer of fibrous connective tissue between them. (b) This connective tissue is continuous with the connective tissue of both submucosa and serosa.

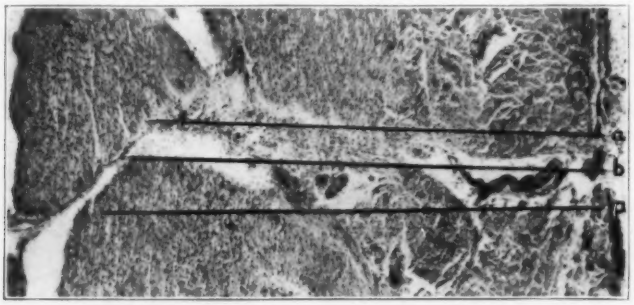

Fig. 6.—Two years after operation. (a) Ends of muscle coats almost in contact. (b) Very thin layer of fibrous connective tissue between them.

tissue between the ends of the muscle coats (Fig. 5). This fibrous tissue is continuous with the submucosa above and the serosa below. At this stage the stomach is normal in size and not distended, while the pylorus feels but little more firm than normal.

The final stage is illustrated by the sections made from a stomach removed at necropsy two years after operation (Fig. 6). The stomach

of this child, who died of aortic stenosis, was 12 cm. long, and the pylorus did not feel abnormally firm. The gastrohepatic omentum was only 1.5 cm. long and very thick. On the under surface of the pylorus, near the greater stomach curvature, there was an irregularly quadrangular area 5 by 4 mm., over which the peritoneum was thickened, but there was no depression. The pyloric circular muscle was 3 cm. thick and the mucosa was normal. On microscopic examination the end result of the healing was seen in an almost complete approximation of the cut ends of the muscle coats with a thin line of connective tissue between them.

DISCUSSION

The healing of the wound in the pylorus made by the Fredet-Rammstedt operation is brought about by the connective tissue of the serous and submucous coats of the stomach. The unstriped muscle cells of the cut muscle layers take no active part in the healing process, as evidenced by the absence of division among these cells. The raw, cut muscle edges and the exposed layer of submucosa which protrudes into the gap between them become covered by a thin layer of delicate granulation tissue, which, by the ninth day, has become cellular fibrous connective tissue. By the contratction of this layer of fibrous connective tissue and the relaxation of the unstriped muscle, the edges of the wound are gradually brought into contact and the pylorus relaxes. In from nine to thirteen days after operation the wound has healed completely, though the site of operation still shows a very evident depression. In twenty-five days this depression has become gradually less, and in six weeks only a delicate scar remains. In sixteen months a very thin linear scar was present. In two years the scar was scarcely visible. Within two weeks after operation the pylorus feels softer than it had felt at operation, and in twenty-five days the stomach is normal in size and the pylorus but slightly firmer than normal. This is in contrast with the condition of the pylorus after gastro-enterostomy, where Dr. Holt [1] found it quite unchanged in thickness from six months to two years after operation.

SUMMARY

It has been shown that the lesion in hypertrophic pyloric stenosis is a hyperplasia of the unstriped muscle cells of the circular coat, while the connective tissue is not increased.

After the Fredet-Rammstedt operation healing is brought about by the cells of the serosa and submucosa, but the unstriped muscle cells take no part in the process.

The wound in the pylorus is healed within nine days. The pylorus has become relaxed within two weeks. The stomach has returned to

1. Holt, L. Emmett: J. A. M. A. **68**:1517 (May 26) 1917.

its normal size within a month and the gap between the cut ends of the muscle coats has practically disappeared in six weeks. In two years only a thin line of connective tissue fibers separates these two muscle ends, and the stomach is quite normal.

In contrast to the operation of gastro-enterostomy which leaves the pylorus unchanged, the Fredet-Rammstedt operation cures the pyloric lesion.

The cases in this series came from the medical service of Dr. Holt and from the surgical service of Dr. Downes, to both of whom I am indebted for the use of the material.

THE VITAMIN REQUIREMENT OF VARIOUS SPECIES OF ANIMALS

III. THE PRODUCTION AND CURE OF XEROPHTHALMIA IN THE SUCKLING

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It is a well known fact that vitamin A is necessary in the diet if normal growth and reproduction shall take place. In the absence of this particular dietary factor a condition known as xerophthalmia or keratomalacia results. It is equally well known that the higher animals cannot synthesize this vitamin and that they must depend, therefore, on green plant tissue as the ultimate source of the vitamin. During the past year some work has been done demonstrating that the quantity of this vitamin in milk will vary with the quantity of vitamin A in the diet.[1] This is to be expected since the animal cannot synthesize this unknown substance, and consequently if the vitamin is not present in the diet the mother cannot secrete it into the milk.

Andrews[2] showed that the milk of a mother whose children had died from beriberi, and whose diet was, therefore, presumably deficient in vitamin B, produced polyneuritis in suckling pups. It must be remembered, however, in this connection that the pups were fed a milk which was not normal for the species, and it may well be that the requirement of pups for vitamin B is different than that of man. We have some data on this point which will form a separate paper of this series.

McCollum[3] has shown that mother rats which were kept on a satisfactory diet until the birth of the young and then were at once restricted to diets lacking vitamin A did not rear the young. He believed it probable that this milk was deficient in quality rather than quantity. He also reported the occurrence of sore eyes in young rats on diets deficient in vitamin A. These sore eyes, however, often occurred after the suckling period, when the young were consuming some of the mother's diet. He also noticed sore eyes on a ration

* Received for publication, Feb. 24, 1922.
* From the Department of Chemistry and the Agricultural Experiment Station, Iowa State College.

1. Drummond, Coward and Watson: Biochem. J. **15**:540, 1921.
2. Andrews: Philippine J. Sc., Ser. B **7**:67, 1912.
3. McCollum and Simmonds: Am. J. Physiol. **46**:275, 1918; McCollum, Simmonds and Pitz: J. Biol. Chem. **27**:33, 1916.

which contained 5 per cent. butter fat, but was deficient in other respects. We have noticed similar symptoms in both rats and rabbits on defective diets, which symptoms could not be relieved by the administration of butterfat. In a few cases the animals became totally blind. McCollum did not attempt to cure this condition by feeding vitamin A to the mother. In his experiments the mother rats no doubt had, at the beginning of the suckling period, considerable reserve of vitamin A in their tissues since they had been upon an adequate diet up until the young were born.

In a previous article we [4] have demonstrated that the rabbit requires more vitamin A than the rat for normal growth and reproduction. The rabbit consistently develops xerophthalmia on diets deficient in vitamin A.[5] This symptom, however, is not to be confused with the occasional occurrence of sore eyes under other unfavorable conditions of environment and diet even though vitamin A is present in the diet. This latter type of sore eyes is probably due to direct infection.

It is possible to feed a rabbit a diet which is below the optimum in its vitamin A content which will produce slow growth with no apparent symptom of dietary deficiency. This kind of diet was fed to six rabbits, five males and one female. The diet had the following composition:

White corn	55
Linseed oil meal	22
Oats	15
Meat meal tankage	5
Supplementary salt mixture	3
	100

This diet has been reported [3] as deficient in vitamin A and capable of producing xerophthalmia in young growing rabbits. The animals mentioned were started on this diet, however, at a weight of 2,000 gm. and were three-fourths grown. After a period of three months they reached an average weight of 2,400 gm. and appeared to be in excellent condition. They were healthy, fat, clear of eye and possessed sleek, fine coats. At this time the female gave birth to five young which she suckled and cared for in a normal manner. Soon after the birth of the young the mother began to lose in weight and developed symptoms of xerophthalmia. Two of the young died before their eyes were opened. The rabbit normally opens its eyes at the age of 10 days. About one week later a third young rabbit died with typical symptoms of xerophthalmia. The two remaining young, which were more vigorous, remained alive with distinct evidence of xerophthalmia. At this point the mother was given in addition to her ration from 1 to 2 gm. butter fat per day. The xerophthalmia in the mother

4. Nelson, Lamb and Heller: Am. J. Physiol. **59**:335, 1922.
5. Nelson and Lamb: Am. J. Physiol. **51**:530, 1920.

cleared up slowly. One of the young (the black shown in the photograph with eyes swollen shut) had become very weak, and died three days later, although the eyes were considerably improved. The other young (grey shown in picture with its eyes almost swollen shut) showed marked improvement in the eye condition and began to grow very rapidly, doubling its weight in thirteen days thereafter. The two young were in very poor condition, had ceased growing entirely, and if butter fat had not been fed to the mother we believe they would certainly have died within twenty-four hours. It seems quite evident that the mother immediately transferred the vitamin A in the butter fat to her own milk and thereby relieved the offspring. During all this time the young were suckling the mother and eating no other food.

The effect of the strain of reproduction on the development of xerophthalmia. The grown rabbit on the left is normal. The doe on the right, on the same ration, developed xerophthalmia in both herself and young, which was cured in both by the administration of butter fat to the doe.

The mature rabbit on the left in the accompanying figure is a representative animal from the group on the above ration. This animal is much more vigorous than the one on the right and the difference in vigor is much greater than is apparent in the picture, which was taken at the time the butter fat feeding was begun. Up until the birth of the young, the two grown rabbits were equally vigorous. The mother rabbit on the right shows xerophthalmia which is indicated by the fact that the eyelids are swollen nearly shut. A typical film had developed on this eye at the time this photograph was taken. It is evident that the strain of reproduction and lactation brought about this symptom of the deficient diet which would otherwise not have become apparent. We are now studying the effect of breeding on the production of symptoms of dietary deficiency using the males of this group of animals on their present diet.

A PECULIAR ERUPTIVE DISEASE OCCURRING IN INFANCY *

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AND

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Zahorsky [1] in 1910, and again in 1913, described a symptom complex under the designation of "roseola infantum," which he believed deserved a nosologic position of its own.

His description of the condition is as follows:

"The patient is almost always a child under 3 years of age who suddenly becomes ill with high fever. The physician is called, and on examination finds nothing to account for the fever. The fever continues but no diagnosis can be made on the second, third or even fourth day. Then the temperature drops to normal, or nearly so, and the child, who has been drowsy and irritable, sits up and commences to play. Coincidentally with the decline in the temperature a morbilliform rash appears on the face and neck and rapidly spreads over the body. The eruption disappears in from twenty-four to forty-eight hours. There are no complications or sequels. No desquamation follows the disappearance of the rash."

This syndrome had been recognized previously [2] but apparently had been classified with the toxic erythemas or, perhaps, as an atypical rubella.

Recently Levy,[3] Veeder and Hempelmann,[4] Greenthal [5] and Westcott,[6] published their observations of, and incited interest in the condition. The clinical descriptions of these authors agree almost completely, though in some minor details their observations vary.

Since February, 1920, one of us (J. H. P.) has observed twenty-one cases of this disorder. To illustrate the condition more fully a typical case will be described.

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* Received for publication, March 24, 1922.

1. Zahorsky, J.: Roseola Infantum, J. A. M. A. **61**:1446 (Oct. 18), 1913; Pediatrics, **22**:60 (Jan.), 1910.

2. Meig and Pepper's Diseases of Children: quoted by Zahorsky.

3. Levy, D. J.: An Eruptive Fever of Unusual Characteristics in Infancy and Childhood, J. A. M. A. **77**:1785 (Dec. 3), 1921.

4. Veeder, B. S. and Hempelmann, T. C.: A Febrile Exanthem Occurring in Childhood (Exanthem Subitum) J. A. M. A. **77**:1787 (Dec. 3), 1921.

5. Greenthal, R. M.: An Unusual Exanthem Occurring in Infants, Am. J. Dis. Child. **23**:63 (Jan.), 1922.

6. Westcott, T. S.: Pseudo-Rubella, Am. J. Med. Sc. **162**:267 (Sept.) 1921.

REPORT OF CASE

History.—Baby R. M., age 8 months, artificially fed, was perfectly well until Oct. 22, 1921. Without prodromata of any sort she became acutely ill. When the child refused a feeding the mother took her temperature and found it to be 103 F., by rectum. Two hours later the temperature was 104 F. The child was irritable, but was not toxic.

Physical Examination.—The physical examination was negative, save for moderate redness of the pharynx and a distinct redness of the posterior quadrants of each ear drum. Urinalysis was negative. A blood count showed: leukocytes 6,600; lymphocytes 82 per cent. Paracentesis of both drums was performed but no discharge followed and there was no drop in temperature.

Clinical Course.—The following morning the temperature was 102.4 F. but mounted toward evening to 104.2 F. The next morning it was 100.4 F. and remained above 101 F. all day. A leukocyte count this day was 5,600 with 87 per cent lymphocytes. On the morning of the fourth day, the temperature was 100.8 F.; by that evening it had fallen to 99 F. (During these days there was no apparent cause for the fever).

At this time a rash appeared, at first on the buttocks, back and chest, and rapidly spread to the back of the neck and scalp and the rest of the trunk. The extremities remained comparatively free. The eruption consisted of closely aggregated pale pink macules or slightly elevated maculopapules. The rash was profuse and confluence led to the formation of several irregular macules of comparatively large dimensions. A few of the lesions possessed urticarial features.

The temperature remained normal from the time of the appearance of the eruption, and thereafter the patient appeared as well as before the illness began.

The eruption reached its height in twenty-four hours, and involuting rapidly, disappeared in another twenty-four hours. No desquamation ensued.

ANALYSIS OF CASES

A picture of the symptomatology from the cases observed is as follows:

Onset.—This was abrupt in all cases, the child being apparently well the day before the illness began. Usually the mother or attendant discovered that the child was warmer than usual, and on taking the temperature, found it to be from 101 to 105 F. by rectum. Fretfulness and irritability were almost invariably present. Prostration was lacking, as well as gastro-intestinal symptoms.

Fever.—The fever mounted rapidly, reaching as high as 105 F. on the first day, but usually reached its maximum on the second or third day. It continued high, with moderate matutinal remissions for from three to five days, when it dropped suddenly to normal or subnormal. Practically all cases pursued the same febrile course. In an occasional case, the fever fell by lysis.

Pulse and respiration were in normal ratio to the temperature.

Eruption.—With the fall in temperature a rash appeared. It was first noted most often either on the buttocks or on the sides of the neck, beginning as discrete macules from 2 to 3 mm. in diameter. It appeared rapidly on other parts, and at its height was usually most

profuse on the trunk, and least intense on the extremities. Typically, it presents a distinctly morbilliform aspect. The lesions are pink to rose colored, fairly well defined, either absolutely level with the sound skin, or occasionally slightly raised maculopapules. They may be entirely discrete, but in some cases presenting a profuse rash confluence occurred, with the formation of lesions several centimeters in dimensions. No enanthem was ever noted. The efflorescence reached its height in twenty-four hours, lasted another day, and disappeared without desquamation.

Physical Findings.—Repeated examinations failed to furnish adequate cause for the fever. In one case there was a distinct redness of the posterior half of each ear drum, and in several other cases there was

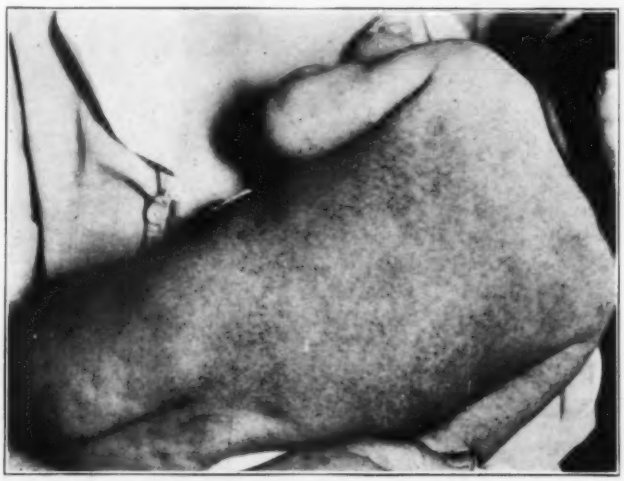

Fig. 1. Baby B., aged 4 months. White blood cell count, 5,200; lymphocytes, 86 per cent. Typical rash appeared on fourth day and disappeared entirely on sixth day. No desquamation.

moderate congestion of the pharynx, tonsils, and soft palate. The lungs and heart were normal, as were the other viscera. There was no adenopathy.

Laboratory Examinations.—Twenty-two blood counts were made in eighteen cases. The highest leukocyte count was 7,800 and the lowest 4,800. Four counts were between 4,500 and 5,500; thirteen between 5,600 and 6,500, and five between 6,500 and 8,000.

In two cases the lymphocytes were between 65 and 75 per cent.; in seventeen cases between 76 and 85 per cent., and in three cases more than 85 per cent.

Leukopenia with lymphocytosis occurred in all of our cases in which the blood was studied. These findings occur at all times during the pre-

eruptive stage, and in conjunction with the clinical symptoms present a picture which is definite and characteristic. Veeder and Hempelmann and Greenthal likewise noted the leukopenia and lymphocytosis, which seems to be an essential part of the syndrome.

In one case a blood culture was negative. All urinalyses were negative, save for minor transitory changes, such as occur in any febrile condition.

Complications.—There were none.

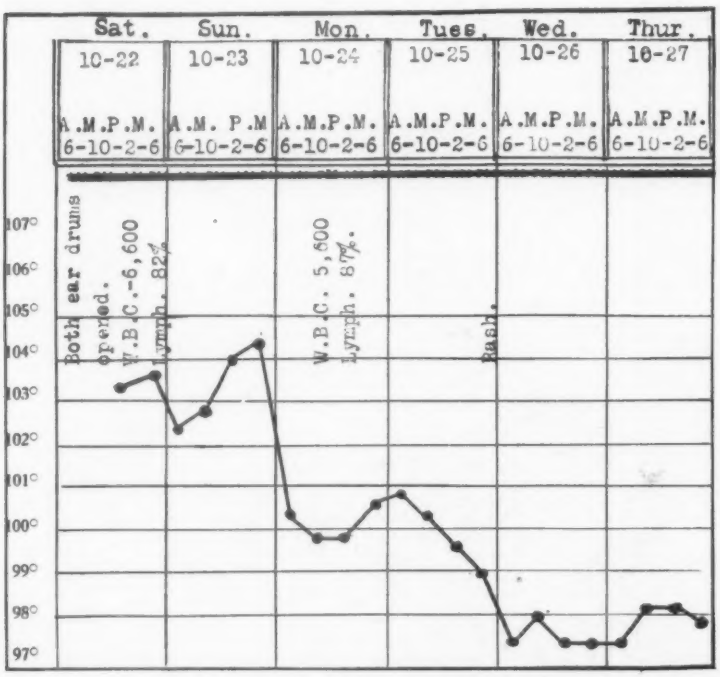

Chart 1.—Temperature chart of Baby R. M., illustrating fall of temperature by lysis.

Age Incidence.—The youngest patient was 4 months of age; the oldest 2 years.

Sex.—Ten patients were males, eleven were females.

Feeding.—Fourteen patients were completely artificially fed; seven received both breast and bottle. None was entirely breast fed.

Communicability.—In no instance was there evidence of contagion, nor have two cases occurred in the same family. There has been no recurrence.

Diagnosis.—In the preeruptive stage, otitis media, influenza, concealed pneumonia, typhoid and pyelitis are suspected, but can be ruled

out by appropriate examination as well as by the further course of the disease.

Of the exanthems only rubella and measles need be considered seriously. The later can be excluded by the absence of catarrhal symptoms and Koplik spots; by the continuance of fever after the appearance of the eruption, and by desquamation. Rubella has a short prodromal period and the fever rises with the eruption. There is postcervical adenopathy and desquamation. In each of these diseases contagiousness is a feature.

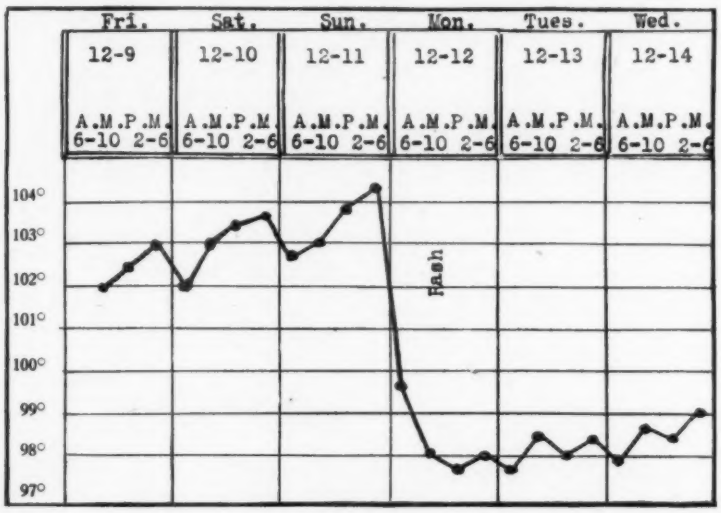

Chart 2.—Temperature chart of Baby B—showing fall of temperature by crisis.

Toxic erythemas may be considered. The rash in this condition may closely simulate the one under consideration, but in toxic erythema, a definite preeruptive stage is lacking. Drug rashes have been eliminated by the history. The fact that the eruption is noncontagious has led us to consider seriously an allergic etiology. We contemplate doing protein sensitization tests as the opportunity arises.

DISCUSSION

Our own experience and that of others leads us to believe that this disorder is a definite clinical entity. The outstanding features are the abrupt onset, the high fever of from three to five days duration without apparent cause, and the appearance of a morbilliform rash coincident with a critical fall of temperature to normal. Additional points of distinction are the apparent non-contagiousness, and the predilection of the disease for infancy. Moderate leukopenia and lymphocytosis appear to be the only significant laboratory findings.

In reviewing the reports of others, we have noted the practically complete accord of all observers as to the clinical course of the disease. There are, however, some discrepancies in the observations which should be noted. For instance, Zahorsky, Westcott, and Levy found enlargement of the superficial cervical lymph nodes, especially the posterior group, in a large majority of their cases. Veeder and Hempelmann, Greenthal and ourselves have not observed any significant adenopathy.

Veeder and Hempelmann, and Greenthal noted very slight desquamation in a few of their cases, while other observers are unanimous in stating that it is absent. In our experience desquamation has never followed the involution of the eruption.

CONCLUSIONS

The pertinent facts of twenty-one cases of an unusual disorder occurring in infancy and childhood have been recorded.

This condition is distinctive and appears to be a clinical entity. We are able to confirm the findings of others that leukopenia and lymphocytosis occur with such uniformity as to be of significance. We have, likewise, noted an entire lack of contagiousness. The etiology is unknown.

THE VALUE OF THE INTRACUTANEOUS TUBERCULIN TEST IN EXTENSIVE TUBERCULOSIS *

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The belief is quite general that the skin hypersensitiveness to tuberculin is frequently lost in the presence of an overwhelming tuberculous infection, such as general miliary tuberculosis and tuberculous meningitis. This belief is based on repeated statements to that effect in textbooks and articles dealing with the tuberculin skin test. Since we accept the fact that skin hypersensitiveness to tuberculin means that there is a focus of tuberculous infection somewhere in the body, if the reaction is frequently lost in one of the forms of tuberculosis in children in which diagnosis is most difficult, i. e., miliary tuberculosis, then the test loses much of its importance.

The statistics on the tuberculin test, especially in children, are based mainly on the results obtained with the Pirquet skin test. Hess [1] tested twelve cases of tuberculous meningitis and found 17 per cent. positive. Dunn and Cohen [2] tested 120 cases of miliary tuberculosis and tuberculous meningitis, with 59.8 per cent. positive. Meyers [3] tested 105 cases of tuberculous meningitis with 63 per cent. positive. From these figures it appears that in generalized tuberculosis negative reactions with the most commonly used test are obtained in 40 per cent. of the cases. On the basis of the Pirquet test there is thus some ground for the belief expressed above.

It is apparent from the literature that with the method extensively utilized by Hamburger [4] (Stichreaktion of Escherich—a subcutaneous injection method) a greater number of positive results are obtained in the presence of severe tuberculosis than by the cutaneous method.

We determined to use the intracutaneous method of Mantoux [5] which was devised as long ago as 1908, but has been comparatively little used with children, except by Jeanneret,[6] chiefly as a therapeutic method. As usually employed, it has given positive results hardly better

* Received for publication, March 3, 1922.

* From the Department of Pediatrics, the Johns Hopkins University and the Harriet Lane Home, the Johns Hopkins Hospital.

1. Hess, J. H.: M. Clinics N. America **1**:1357, 1918.
2. Dunn, C. H., and Cohen, S. A.: Am. J. Dis. Child. **21**:187, 1921.
3. Meyers, A. E.: Am. J. Dis. Child. **9**:427, 1915.
4. Hamburger, F.: Die Tuberkulose des Kindesalters, Leipzig and Wien., Franz Deuticke, 1912.
5. Mantoux, C.: Compt. rend. Acad. d. Sc., Par. **147**:355, 1908.
6. Jeanneret, L.: La Tuberculose de l'Enfant, Paris, 1915.

in frequency or regularity than the Pirquet cutaneous test. Bass'[7] experience is an exception to this. He found the intracutaneous test definitely more satisfactory than the Pirquet cutaneous test in detecting mild degrees of tuberculous infection in apparently well children. Certainly, the intracutaneous test is sensitive, and with care and experience yields accurate results. We employed it on the suggestion of Dr. A. K. Krause that the ability of the tuberculous to react to tuberculin in overwhelming tuberculous infection is not lost but merely depressed, because the Mantoux method allows the use of accurately measured amounts of tuberculin. It is thus possible to begin with a small amount and increase the amount at subsequent injections, provided there is no positive reaction with the smaller quantity.

For the tests we used old tuberculin obtained from Dr. E. R. Baldwin at the Saranac Laboratory and from Dr. A. K. Krause's laboratory at Johns Hopkins Hospital. Dilutions were made in 0.85 per cent. sterile saline solutions with 0.25 per cent. phenol as a preservative, and graded so that 0.1 c.c. of the solution contained the amount to be injected. The solutions were kept in dark bottles in the refrigerator and were made fresh once a month. They remained sterile. The amounts used were 0.01 mg., 0.1 mg., 1 mg., and in a few instances more than 1 mg. As a control solution we used equivalent amounts of glycerin broth diluted as above with phenol preservative and of the same concentration as the glycerin broth of the old tuberculin. This is the only solution that can be considered a true control. The tests were made and were read at the end of twenty-four and forty-eight hours. A definite erythema or erythema and induration 0.5 cm. or more in diameter was considered positive, provided the control was entirely negative.

The amount of tuberculin advisable to use for the first test depends on the condition of the patient. Krause[8] and Willis[9] found that a general reaction of an anaphylactic character can be produced in nontuberculous guinea-pigs after repeated injections of tuberculin but never was a local (tissue) reaction obtained. This anaphylactic reaction bore no relation to the general tuberculin reaction and must not be confused with it. Similarly Hamburger[4] was never able to obtain a local reaction from tuberculin in the nontuberculous human being. He gave as much as 1,000 mg. with negative results. On the other hand, great care must be observed when tuberculosis is suspected, for not only may the arm become swollen and painful but occasionally sloughing occurs at the point of injection when too large an amount is given. Also, the excitation of a general reaction with fever and an activation of the

7. Bass, M. H.: Am. J. Dis. Child. **15**:313, 1918.
8. Krause, A. K.: J. M. Research **19**:361, 1911.
9. Krause, A. K., and Willis, H. S.: Am. Rev. Tuberc. **3**:153, 1919.

tuberculous condition at the focus or foci of infection may occur. For these reasons the amount for the initial injection should be small, and then, if no reaction takes place, the next higher concentration may be given, and so on. For routine tests with children we used 0.01 mg. as an initial injection. Some patients will react to 0.001 mg., but a violent reaction following the injection of 0.01 mg. is most uncommon. In order to obviate unnecessary tests, 0.01 mg. was usually given as a routine measure for the initial injection when the forms of tuberculosis which present in the patient the greater skin sensitiveness were suspected, namely, tuberculous conjunctivitis or keratitis, skin manifestations, superficial glandular, osseous, early active pulmonary, pleuritic or renal. The next higher concentration (0.1 mg.) was employed as the initial injection only when a depression of skin sensitiveness might be assumed, for instance, with generalized tuberculosis and tuberculous meningitis.

In order to compare the results of our intracutaneous tests with those of the Pirquet cutaneous test, we did Pirquet tests in most instances at the same time as the intracutaneous tests. For statistical purposes we have included the results of Pirquet tests upon previous cases of miliary tuberculosis and tuberculous meningitis when the diagnosis had been confirmed by necropsy or by finding tubercle bacilli. The results of both tests are presented in Tables 1 and 2.

TABLE 1.—CASES OF MILIARY TUBERCULOSIS INCLUDING TUBERCULOUS MENINGITIS IN WHICH TUBERCULIN SKIN TESTS WERE PERFORMED

	Pirquet			Per Cent.	Intracutaneous			Per Cent.
	No.	+	0	+	No.	+	0	+
Miliary tuberculosis with meningitis	113	79	64	55.2	53	49	4	92.4
Miliary tuberculosis without meningitis	40	15	25	37.5	19	14	5	73.6
Total	183	94	89	51.3	72	63	9	87.5

TABLE 2.—NUMBER OF POSITIVE REACTIONS OBTAINED IN MILIARY TUBERCULOSIS INCLUDING TUBERCULOUS MENINGITIS WITH GRADED AMOUNTS OF TUBERCULIN ADMINISTERED INTRACUTANEOUSLY

Amount in Mg.	0.01	0.1	1.0	More Than 1.0
Number positive	12	48	15	5
Number negative	12	12	1	0
Percentage positive	50	80	93.7	100

It should be emphasized that these tests were performed on patients with advanced generalized tuberculosis and contrary to the belief of Jeanneret [6] and others that under such circumstances the sensitiveness to tuberculin usually disappears five days, a week, or more before death;

most of our intracutaneous tests happened to be performed and reactions obtained during the four days prior to death. As many as 41 per cent. were obtained during the last two days before death and 22 per cent. on the last day of life.

Of those to whom 0.01 mg. was given, 50 per cent. reacted (Table 2) which is about the same percentage that reacts to the Pirquet skin test. By doing parallel Pirquet and intracutaneous tests on all patients admitted to the hospital, we received further convincing evidence that the sensitiveness to tuberculin is quantitative and that the frequency of reaction after the employment of the Pirquet cutaneous test is nearly the same as that with 0.01 mg. of tuberculin given intracutaneously.

Finally, it is but fair to the intracutaneous test to say that the nine negative tests (Table 1) were obtained in patients who either did not live long enough or did not remain in the hospital long enough to receive more than the smaller amount of tuberculin. We feel that had it been possible to give them the higher concentrations, all or nearly all would have reacted, for as seen in Table 2 all except one who received as much as 1 mg. reacted, and the few to whom we gave more than 1 mg. gave marked reactions. Only occasionally, in a patient with far advanced generalized tuberculosis and extreme emaciation, was more than 1 mg. tuberculin ever required to excite a reaction.

CONCLUSIONS

1. In miliary tuberculosis and tuberculous meningitis in infants and children the Pirquet cutaneous test was positive in just over 50 per cent. of our cases.

2. A failure to react to the Pirquet test in miliary tuberculosis and tuberculous meningitis does not mean a loss but only a depression of skin sensitiveness to tuberculin.

3. The tuberculin test is quantitative and the Pirquet cutaneous test is equivalent to about 0.01 mg. tuberculin given intracutaneously.

4. The intracutaneous test is more sensitive and as opposed to the Pirquet test it not only affords a method of accurately measuring the amount of tuberculin given, but enables one to increase the amount at will.

5. If a high enough concentration of tuberculin is given intracutaneously, a positive reaction will be obtained in practically all cases of tuberculosis.

THE BACTERIOLYSANT THERAPY OF BACILLARY DYSENTERY IN CHILDREN *

THERAPEUTIC APPLICATION OF BACTERIOLYSANTS; D'HERELLE'S PHENOMENON

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It has been demonstrated by d'Herelle and others [1] that if a small portion of feces from a dysenteric convalescent or even from a normal person is inoculated in a flask of bouillon, and this mixed culture is passed through a Berkfeld filter, the resulting sterile filtrate, when added to young cultures of dysentery and other bacilli, will kill and dissolve the organisms. If a portion of this dissolved culture is, in turn, added to another young dysentery culture, the organisms will again be killed and dissolved. This phenomenon can in this way be reproduced for innumerable successive generations. The names bacteriophage, bacteriolysant and lytic agent have been given to these filtrates. When they are injected intravenously and subcutaneously into rabbits and other animals, no harmful effects are produced. These animals develop antibodies for the organisms against which the filtrates are active. It was obvious to many observers that these filtrates which would kill and dissolve dysentery bacilli in vitro, which were nonpathogenic and would immunize animals, should be tried therapeutically in clinical cases of dysentery. However, the question arises as to whether the administration of an antidysentery bacteriophage to dysentery patients might not possibly be harmful. The intestinal lesions of dysentery are probably caused by an endotoxin, and it would seem logical to assume that if dysentery bacilli in the intestinal tract were killed and dissolved as the result of the administration of a bacteriophage, a large amount of endotoxin would be liberated. Nevertheless Kabeshima and others [1] have demonstrated that injections of an antidysentery bacteriophage into rabbits infected with dysentery bacilli are harmless. I have injected large amounts of these filtrates into a rabbit and am convinced that they are innocuous. Inasmuch as Flexner dysentery in children is one of our worst diseases, and as

* Received for publication Feb. 23, 1922.

* From the Department of Pediatrics, the Johns Hopkins University and the Harriet Lane Home, the Johns Hopkins Hospital.

1. A summary of the literature and a complete bibliography is given in Davison, W. C., Bibliographic review of bacteriolysants (d'Herelle's phenomenon), Abstr. Bacteriol., Baltimore, 1922 (in press).

serotherapy [2] and our present treatment are ineffectual in reducing the high mortality, I felt justified in cautiously proceeding with bacteriolysant therapy during the summer of 1921.

Bacteriolytic filtrates active against one or more strains of Flexner bacilli were obtained by d'Herelle's method. The bacteriolytic activity of these filtrates was tested in eight instances against the organism isolated from the patients' stools and in seven the filtrates were found to be active. The method of obtaining these filtrates and testing their activity is described elsewhere.[3]

These filtrates were administered to twelve infants, aged from 2 months to 4 years, suffering from bacillary dysentery (Flexner). Clinically these children represented typical cases of this disease.[4] *B. dysenteriae* (Flexner), and by that I refer to the whole group of mannite fermenting dysentery bacilli,[5] were isolated from the stools of ten of the twelve patients. The individual dose of the bacteriolysant was from 5 to 198 c.c. and was given from one to ten times. The interval between doses was from four to twenty-four hours. The total amounts administered to any one child varied from 5 to 1,381 c.c. Seven children drank the filtrates from a cup or a nursing bottle (the taste is very similar to that of broth); in five cases the filtrates were introduced by rectum with a high enema tube; to two patients they were given by gastric gavage together with the feedings of protein milk. In two infants, in addition to rectal administration, the filtrates were introduced into the stomach through a constant drip nasal tube together with the saline that was being used to maintain the body fluid.

Nine of these twelve patients had severe infections and seven of them died, a mortality of 78 per cent. Three had moderate infections and none died, making a total mortality for the twelve cases of 58 per cent. These figures are practically identical with those we have previously published [2] for severe and moderate dysenteric infections in children, both untreated cases and those treated with subcutaneous and intramuscular injections of antidysenteric serum. In no instance did the patient seem any the worse for the treatment. One patient's stools decreased in number after rectal treatments with a filtrate but inasmuch as the bacteriolytic filtrate used, though active against another strain of the Flexner bacillus, had but slight lytic action on the organisms isolated from this patient's stools, it may be concluded that the improve-

2. Josephs, H. W., and Davison, W. C.: The Serotherapy of Bacillary Dysentery in Children, J. A. M. A. **77**:1863 (Dec. 10) 1921.

3. Davison, W. C.: Observations on the Nature of Bacteriophages, Bacteriolysants, Lytic Agents, d'Herelle's Phenomenon, Proc. Soc. Am. Bacteriologists, Dec. 29, 1921; J. Bacteriol., 1922 (in press).

4. Davison, W. C.: Bacillary Dysentery in Children, Bull. Johns Hopkins Hosp. **21**:225, 1920.

5. Davison, W. C.: Divisions of the So-called Flexner Group of Dysentery Bacilli, J. Exper. M. **32**:651, 1920.

RESULTS OF ADMINISTRATION OF DYSENTERY BACILLUS BACTERIOLYSANT

Case No.	Age	Race	Stool Culture	Degree of Severity of Infection	Method of Administration of Bacteriolysant	Days After Onset on Which First Dose of Bacteriolysant Was Given	Number of Doses of Bacteriolysant Given	Interval Between Doses, Hours	Amount of Each Dose, C.c.	Total Amount of Bacteriolysant Given, C.c.	Lytic Activity of Bacteriolysant Against Dysentery Bacillus Isolated from Patient's Stool	Duration of Disease, Days	Final Outcome of Patient	Effect of Bacteriolysant
29271	2 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection	11	2	8	34-35	80	Slight	17	Recovered	No effect
29556	15 mos.	White	Negative	Severe	By mouth (bottle)	16	2	24	36-60	96	Not tested	20	Died	No effect
29627	12 mos.	White	B. dysenteriae (Flexner)	Severe	By mouth (gavage)	13	3	8-12	80-100	280	Strong	15	Died	No effect
29717	12 mos.	Colored	B. dysenteriae (Flexner)	Severe	By mouth (bottle and gavage)	20	3	4-16	45	135	Not tested	21	Died	No effect
29010	6 mos.	Colored	B. dysenteriae (Flexner)	Severe	Rectal injection and nasal drip	13	4	6-12	55-126	323	Strong	14	Died	No effect
29565	14 mos.	White	B. dysenteriae (Flexner)	Severe	By mouth (bottle)	26	4	7-12	30-60	195	Strong	39	Died	No effect
29272	2 mos.	White	Negative	Severe	Rectal injection	11	6	8-17	25-40	170	Not tested	13	Died	No effect
29413	7 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection	6	6	5-24	25-50	250	Slight	24	Recovered	Apparent benefit
29569	3 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection and nasal drip and by mouth (bottle)	8	10	6-24	55-198	1,381	Strong	18	Died	No effect
29456	9 mos.	White	B. dysenteriae (Flexner)	Moderate	By mouth (bottle)	16	1	....	40	40	Not tested	21	Recovered	No effect
29022	2½ yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	16	1	....	72	72	Strong	?	Recovered	No effect
29700	4 yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	1	1	....	5	5	Negative	9	Recovered	No effect

ment was due to the cleaning of the lower colon by the rectal irrigation rather than to the bacteriolytic action of the filtrate. In none of the other children was there any apparent effect on the course or duration of the disease. No systematic study was made to determine the effect of the treatment on the rate of disappearance of the dysentery bacilli from the stool. In Case 29,569, *B. dysenteriae* (Flexner) were isolated from the stools twenty-four hours after the last of ten doses of bacteriolysant. The total amount of filtrate given this patient was 1,381 c.c. It is interesting to note that the bacteriolysants used in this case lysed the dysentery bacilli isolated after the treatment in higher dilutions than the organism isolated shortly after the onset of the disease, so that is fair to assume that this patient did not die because his organisms became resistant to the filtrates.

The failure of bacteriolysant therapy in this series may possibly be explained on the ground that the treatment in the majority of the cases was commenced late in the disease. The only two patients treated within the first week after the onset of the disease recovered. However, this criticism is met by the large amounts of filtrate used, coupled with the fact that two-thirds of the deaths from bacillary dysentery in children, whether treated or not, occur within the first twelve days [2] and that patients serviving that period have a much better chance of recovery.

D'Herelle,[1] on the other hand, has reported striking cures from bacteriophagic therapy in seven adults suffering from dysentery as well as in animals afflicted with various infections. Larger series alone will demonstrate the practical value of bacteriolysants.

CONCLUSION

As far as can be judged from this limited series of cases of bacillary dysentery in children, in which bacteriolytic filtrates in amounts of from 5 to 1,381 c.c. were administered, bacteriolysant therapy did not influence the mortality or the course of the disease.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD*

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ST. LOUIS

(Concluded from page 469)

GENERAL OBSERVATIONS ON HEREDITARY SYPHILIS

Stoll [148] gives a review of the various clinical signs of the disease—naturally a subject to which but little has been added. He makes some timely remarks on the ease with which the smaller signs may be missed, and the Wassermann test be omitted as a result. Stoll describes a sign which might well be due to other conditions, but which he has frequently encountered in hereditary syphilis—namely, an increase in the normal carrying angle of the elbow, which he has called the "knock-knee elbow," and which is due to overgrowth of the internal condyle of the humerus. It occurs sometimes with limitation of extension. Other general discussions of the symptomatology of hereditary syphilis are those of Beeson [149] and of Langstein.[150]

MISCELLANEOUS OBSERVATIONS

Thiroux [151] notes that the influence of syphilis on the development of athrepsia is not a new question; but that the existence of athrepsia exclusively syphilitic has not been sufficiently emphasized. His studies were made in Indo-China, where syphilis is extremely common. The manifold causes of athrepsia in such a population are given full weight. He reports one breast fed baby (with an apparently healthy mother) practically moribund from vomiting and diarrhea. Dramatically rapid improvement followed intensive antisyphilitic treatment without other change. He adds the report of a similar case, calling attention to the possibility, especially in Indo-China, of purely syphilitic enteritides.

Almkvist [152] found that the weight gradually declines under mercurial treatment and increases under arsphenamin. He strongly urges especial attention to diet in cases receiving mercury.

Blechmann [153] presents evidence to show that inherited syphilis is often responsible for different forms of jaundice in infants, hitherto

* From the Department of Pediatrics, Washington University.

148. Stoll: J. A. M. A. **77**:919 (Sept. 17) 1921.
149. Beeson: Illinois M. J. **40**:222 (Sept.) 1921.
150. Langstein: Deutsch. med. Wchnschr. **47**:449 (April 21) 1921.
151. Thiroux: Bull. de l'Acad. de méd., Par. **84**:215 (Nov. 9) 1920.
152. Almkvist: Hygiea, Stockholm, **83**:363 (June 16) 1921; abstr. J. A. M. A. **77**:416 (July 30) 1921.
153. Blechmann: Nourrisson **8**:145 (May) 1920.

ascribed to other causes, or even regarded as physiologic. The occurrence of jaundice, in his opinion, calls for scrupulous investigation for syphilis.

Gelston [154] says that syphilis without doubt plays a part, and an important one, in certain cases of hemorrhagic disease of the new-born.

Castex and del Valle [155] regarded hereditary syphilis as a frequent, perhaps the most frequent, cause of membranous perienteritis and analogous conditions. The intestinal stasis in these cases is attributed to endocrine disturbances secondary to syphilis; and the resulting chronic inflammation of the colon spreads to the surrounding serous membrane. Surgery in such cases should, of course, be limited to those which resist antisyphilitic treatment, or in which adjacent organs become inflamed.

An unusual case report is that of a girl, aged 9, studied by Maggesi.[156] She developed attacks of high fever lasting for two or three days, with intervals of a few days. There was no chill, no profuse sweating, and the general condition continued fair. An eruption finally accompanied the attacks and retrogressed with them. The positive Wassermann and negative malaria search were confirmed by cure under mercurial treatment.

Three case reports by Lornholt [157] are of interest as showing the necessity for vigilance for the possibility of infants acquiring syphilis from the mother, at birth. He cites from the literature two cases of infants infected by the mother at birth. In these and in his own three cases, the mother was infected late in pregnancy, and at confinement had open sores on the pudenda. In four infants chancres were found on the scalp; in the fifth case, on the cheek. The chancres were multiple in all cases. The maternal secondaries were undetected until confinement or shortly afterward. Handowsky [158] reports a typical chancre on the lip of an infant 11 months old, with rapid improvement on antiluetic treatment.

Ugon [159] gives interesting data on three women who developed multiple mammary chancres while nursing children who were not suspected of syphilis. One of the women infected another child she was nursing at the time.

PATHOLOGIC STUDIES

Warwick's necropsy findings in 200 new-born infants have already been mentioned.[12] Browne's findings in a series of 200 still-births

154. Gelston: Am. J. Dis. Child. **22**:351 (Oct.) 1921.

155. Castex and del Valle: Surg., Gynec. & Obst. **31**:160 (Aug.) 1920.

156. Maggesi: Riv. critica di clin. med. **22**:253 (Aug. 5) 1921; abstr. J. A. M. A. **77**:1211 (Oct. 8) 1921.

157. Lornholt: Ann. de dermat. et syph. Series **6—2**:17 (Jan.) 1921.

158. Handowsky: Ztschr. f. Kinderh. **28**:216 (March 21) 1921.

159. Ugon: Arch. Latino-Amer. de Pediat. **14**:241 (May and June) 1920; abstr. J. A. M. A. **75**:1099 (Oct. 16) 1920.

have also been discussed.[11] In his discussion of pathology, he emphasizes the lesions in the thyroid (especially fibrosis), the thymus (also fibrosis), the lung, and the liver (periportal cirrhosis). In his later article,[160] he reports splenic enlargement (virtually diagnostic when present) in only five cases, the largest weighing 55 gm. In all cases the enlargement was associated with periportal cirrhosis of the liver. The *spirochaeta pallida* was found in eight cases of fourteen known syphilitic macerated fetuses. In twenty-one fresh fetuses, it was found in only one. One of the fresh fetuses in which it was not found was the twin of a macerated fetus in which numerous spirochetes were present. Browne believes that the placenta is virtually of no value in the diagnosis of syphilis in the full time infant; but that it may give strong additional evidence in premature and macerated fetuses.

The phenomenon of "immediate death" in heredosyphilitic infants is discussed editorially,[161] the term immediate death meaning death occurring two or three minutes after birth. The lungs are frequently the seat of inflammatory changes, and the liver and spleen are rarely intact. Ascites is generally present. There are some cases in which the most careful necropsy has failed to reveal any determining cause for sudden death. Bonnet is quoted as believing that the real cause is often the impossibility of pulmonary expansion, on account of the hypertrophy of the abdominal viscera.

An important, exhaustive study of the visceral changes in hereditary syphilis has recently been published by Fraser.[162] The results of his investigations are too numerous and detailed to be abstracted here. His article should be read by every student of the subject.

It is Fletcher's opinion[163] that in hereditary syphilis resistance to other infections is greatly lowered, and he considers this especially true of tuberculosis. He describes the morbid changes in heredosyphilitic kidneys. In the fetus, groups of embryonal cells surrounded by normally developed tissue, and small cell infiltration of the cortex, constitute the common lesions. In infants and older children sclerosis is much more marked.

Rolleston[55] also notes that hereditary syphilis should be considered a factor predisposing to other infections. He believes that multilobular or portal cirrhosis may very frequently be heredosyphilitic in origin.

Lemaire et al[164] present the necropsy findings in a case (age 2 months) of intestinal hemorrhage of syphilitic origin. The examination was negative except in the intestine. In the ileum and jejunum there

160. Browne, F. J.: Edinburgh M. J. **27**:199 (Oct.) 1921.
161. Med. Rec. **100**:946 (Nov. 26) 1921.
162. Fraser: J. A. M. A. **77**:1623 (Nov. 19) 1921.
163. Fletcher: Lancet **1**:630 (March 26) 1921.
164. Lemaire, Blechmann, and Turquety: Nourrisson **9**:104 (March) 1921.

were multiple disseminated ulcers, also hemorrhagic areas, on the intestinal walls, with slight hyperplasia of the involved portion of the gut. There were no lesions of Peyer's patches.

Methods for the demonstration of spirochetes in the tissues are described by Haythorn,[165] by Warthin and Starry,[166] and by Jahnel.[167]

TREATMENT

Prophylaxis.—It is clear from the recent literature that the prophylaxis of hereditary syphilis is obtaining the recognition it deserves. Fundamentally, of course, the prophylaxis of hereditary syphilis is the prophylaxis of the acquired disease. Improving economic conditions, providing better and more available public amusements, sex education—"general uplift," in short—must be given proper weight. But, in the language of Vernes,[168] "until such slowly operating methods can become effective" prophylaxis by medical means must be resorted to. Besides the local measures already in use, the arsphenamin prophylaxis described by Michel and Goodman [169] deserves mention. They have found that the administration of several doses of arsphenamin to patients known to have been exposed to syphilis—i. e., in the incubation period between exposure and initial lesion—is completely successful in preventing the appearance of the disease in many cases.

The subject of syphilis and marriage, discussed by Kleeberg,[170] is, of course, a most important one. His text is a woman of 39, apparently free from signs of syphilis since 1903 when she was given a course of inunctions. She had had fifteen pregnancies, and nearly all the children and fetuses showed inherited syphilis, most severe in the fifteenth child. He insists that every woman with a history of syphilis, regardless of the length of the interval since infection, should be given a course of energetic treatment when she becomes pregnant, unless there is absolute certainty that abortive treatment has eradicated the disease. Hata [171] urges the necessity of educating the public, lay and professional, in the dangers of transmission of syphilis by women with positive Wassermann reactions without symptoms. He also recommends an educational campaign among midwives, thorough treatment of positive cases during pregnancy, insistence on examination of the blood of both partners, and the early treatment of syphilitic babies. Findlay [172] believes that antenatal treatment can best be handled,

165. Haythorn: J. A. M. A. **76**:725 (March 12) 1921.
166. Warthin and Starry: J A. M. A. **76**:234 (Jan. 22) 1921.
167. Jahnel: München. med. Wchnschr. **67**:1263 (Oct. 29) 1920.
168. Vernes: Internat. J. Pub. Health **2**:147 (March-April) 1921.
169. Michel and Goodman: J. A. M. A. **75**:1768 (Dec. 25) 1920.
170. Kleeberg: Med. Klin. **17**:962 (Aug. 7) 1921; abstr. J. A. M. A. **77**:1293 (Oct. 15) 1921.
171. Hata: Internat. J. Pub. Health **2**:354 (July-Aug.) 1921.
172. Findlay: Glasgow M. J. **96**:278 (Nov.) 1921.

and with the least degree of publicity for innocent women, by the family physician. He urges compulsory notification of all stillbirths, miscarriages and syphilitic children. Husten [173] and Browne [11] also urge notification, the latter, however, preferring that notification be voluntary.

Vernes [168] believes that methods like those used at the Institut Prophylactique (founded in Paris, 1916) are of great value, the fact that the records are confidential, the methods thorough, the laboratory facilities ample, making careful observation possible, and "prophylaxis by treatment" a reality. Couvelaire [174] describes a "maternity consultation dispensary," which "gathers the pregnant women and treats them and their fetuses." Attendance there has no stigma, and the women flock to it. Knowlton [175] remarks that the essential factors in preventing syphilis among children are the discovery and proper treatment of adult carriers of the disease—a corroboration of Heagerty's statement [49] that "wrapped up in the word latency is the key to the cure of syphilis" (and to its prevention in children).

Hendry [176] finds that when treatment is begun during pregnancy, the prognosis for the fetus depends on the unknown degree of infection already present in the fetus. In Routh's opinion,[177] if unrestricted infection has been going on in the early ovum or fetus, rapid destruction would result in spite of treatment. Jewesbury [14] found that treatment begun after the seventh month of pregnancy did not prevent the birth of a syphilitic child—though subsequent cure of such a child could be effected more readily. The majority of those in whom treatment was begun not later than the fifth month had children free from syphilis. In Williams' [8] series, the comparative results obtained in treated and untreated mothers were most striking. He says that "There is every reason to hope that in future hereditary syphilis may be practically eradicated in clinics in which the mothers register prior to the middle of pregnancy." Adams,[178] Preuss [179] and Beck [180] submit further evidence of the value of prenatal treatment.

Sauphar [181] urges that as two organisms—mother and child—must be protected, antisyphilitic drugs must be given in larger dosage during pregnancy. He adds that both doctor and patient must remember

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173. Husten: Arch. f. Kinderh. **69**:319 (May 21) 1921; abstr. J. A. M. A. **77**:327 (July 23) 1921.
174. Couvelaire: Gynéc. et Obst. **4**:9 (July) 1921.
175. Knowlton: Pub. Health Rep. **36**:2305 (Sept. 23) 1921.
176. Hendry: Lancet **2**:986 (Nov. 13) 1920.
177. Routh: Lancet **2**:988 (Nov. 13) 1920.
178. Adams: Lancet **2**:990 (Nov. 13) 1920.
179. Preuss: Therap. Halbmonatsh. **35**:306 (May 15) 1921.
180. Beck: Am. J. Obst. & Gynec. **2**:416 (Oct.) 1921.
181. Sauphar: La Médecine **2**:569 (April) 1921.

that it is the syphilis and not the treatment that causes miscarriage; and in the event of abortion, it may be assumed that the treatment has been inadequate or begun too late.

Greenlees [182] cites cases to show the inadequacy of antenatal treatment with mercury and potassium iodid alone, emphasizing the great advantage of combining these drugs with arsphenamin. He also notes that in spite of the absence of further treatment, the majority of the mothers continued to bear nonsyphilitic children. Success in producing a negative Wassermann in the mother seems not to be as complete as that in producing nonsyphilitic children. The author thinks it not incongruous that a woman with a positive Wassermann reaction should give birth to a healthy child. The spirocheticide has easy access to the organism in the highly vascular tissues of the uterus and placenta, though probably the positive Wassermann may be due to organisms inaccessible to the drug and for the same reason harmless to the child. He says it has not been definitely ascertained how late in pregnancy treatment may be begun and success expected.

Rawlins [183] goes so far as to urge antisyphilitic treatment for *all* women giving a history of miscarriages or stillbirths, even with a negative Wassermann. In her experience, collosal sulphur, or sublimed sulphur, or intramine, will help to prevent mercurialism and also to cure the syphilis. In discussing her paper, McKenzie urged that the medical profession teach venereal men and women methods of birth control. In the course of the same discussion, Walker said that rather than birth control, added facilities for treating syphilitic pregnant women were needed.

POSTNATAL TREATMENT; GENERAL OBSERVATIONS

All are agreed that treatment is of practically no avail as far as complete cure is concerned, unless it is given persistently and regularly over a long period of time. The essential part played by the social worker in achieving this end is coming to be more and more recognized. Solomon [184] says that a high percentage of success is secured only by the persistent follow-up and persuasion of the social worker. Without such a follow-up, many families ignore the appeal to report to the hospital. Smith [185] points out that these workers require special training, as they are frequently called on to handle most delicate situations with parents, employers, the courts, probation officers, etc. The financial difficulties in the way of one or other parent bringing children to clinics, are also emphasized by him.

182. Greenlees: Glasgow M. J. **96**:270 (Nov.) 1921.
183. Rawlins: Brit. M. J. **2**:194 (Aug. 7) 1920.
184. Solomon, M. H.: Social Hygiene **6**:93 (Jan.) 1920.
185. Smith, C. M.: Arch. Dermat. & Syph. **4**:723 (Dec.) 1921.

Mrs. B. Marshall [186] urges that parents of syphilitic children be seen by the social worker in the clinic in which the parents are treated, so that the efforts of both doctor and social worker can, if necessary, be combined to impress either or both parents with the necessity of having all the children examined. As might be expected, many mothers, when the situation is explained to them, are willing to cooperate. Others require, when everything else fails, resort to the Juvenile Court. One of the chief difficulties encountered by her was the common one met in trying to get parents to continue the children's treatment after the subsidence of acute manifestations.

Systematic plans of treatment have been outlined by several writers. Space does not allow the presentation of the details of each plan. Engel and Türk [187] do not use intravenous therapy during early infancy on account of the smallness of the veins. They prefer "novasurol" intramuscularly, and also mercury-protoiodid. Intravenous arsenical medication is started after the first six months. Blechmann [188] urges intensive intravenous treatment with novasenobenzol, regardless of the age of the infant.

Fordyce and Rosen [189] give neo-arsphenamin and mercuric chlorid intramuscularly. A special needle for this purpose is described. The mercuric chlorid is put up in palmatin to favor its slow absorption (in three or four days). The authors claim that if neo-arsphenamin is given deeply enough into the muscle, abscesses and infiltrations can be avoided.

Jeans [190] describes the method used in his clinic in the Washington University Dispensary. All drugs are proportioned to body weight. The treatment consists of mercury with chalk by mouth, daily; weekly intramuscular injections of mercuric bichlorid (1 per cent. solution); and a bimonthly course of three injections of arsphenamin intravenously. An important feature of this method is that infants must continue such a routine at least one year, and older children at least two years, regardless of what the Wassermann reaction may be. The same treatment is continued longer if indicated by the Wassermann or the clinical signs. Arsphenamin therapy is preceded by examination of the cerebrospinal fluid, to prevent a Herxheimer reaction in the central nervous system. Intraspinal treatment (Swift-Ellis method) is resorted to in cases of infection of the central nervous system not responding to ordinary treatment.

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186. Marshall, Mrs. B.: Report of Social Worker for Syphilitic Children, Washington University Dispensary and St. Louis Children's Hospital, December, 1920.

187. Engel and Türk: Therap. Halbmonatsh. **35**:242 (April 15) 1921.

188. Blechmann: La Médecine **2**:137 (Nov.) 1920.

189. Fordyce and Rosen: J. A. M. A. **75**:1385 (Nov. 20) 1920.

190. Jeans: J. A. M. A. **76**:167 (Jan. 15) 1921.

Findlay [191] condemns the intramuscular administration of the arsenicals because of the likelihood of sloughing and necrosis. He adds that mothers always ask that arsphenamin and allied compounds be given intravenously. He advises against giving arsphenamin by way of the longitudinal sinus, on account of the dangers involved. "Neokharsivan" is the arsenical used by him. Fleming [192] especially recommends the use of the scalp veins for intravenous therapy. He emphasizes the recognized fact that the younger the patient the greater is the likelihood of cure.

Morton Smith [193] denies the statement that arsphenamin has failed in the treatment of interstitial keratitis, and gives case reports to prove his point. In none of his cases was the eye condition aggravated by the arsphenamin. With regard to optic atrophy, Stokes [194] agrees with Ehrlich that arsphenamin is contraindicated in some cases of simple primary optic atrophy. He also agrees with Smith as to the excellent results obtained with arsphenamin in cases of keratitis. Stokes urges that deafness in hereditary or acquired syphilis should be treated no matter how long it lasts, for he has seen patients benefited occasionally. He corroborates Jeans' view that the expert seldom or never has need to use any other than the intravenous route for the administration of arsphenamin. The idea of the Welander homes for the treatment of cases of hereditary syphilis is strongly supported by Stokes. Jewesbury [14] describes the course of treatment with novarsenobillon which he has used with success. Its effects on individual symptoms are noted. McKenna [195] has used virtually all the arsenicals including galyl. He now uses neokharsivan because of the infrequency of toxic reactions. In the discussion of McKenna's paper, Harrison said that neo-arsphenamin gave better therapeutic results than arsphenamin; but that neither could be given intramuscularly without causing a great deal of pain. On this account he welcomed sulfarsenol because it causes no more pain than the mercurials when given intramuscularly. Harrison urges continuation of treatment in cases with a persistently positive Wassermann reaction. He believes that under treatment the tissues "form the habit" of elaborating the substances discovered in the Wassermann reaction. According to Gralka,[196] who gives his results with 410 children, when the treatment is inadequate, a positive Wassermann may be obtained from fifteen to twenty years later.

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191. Findlay: Brit. M. J. **2**:197 (Aug. 7) 1920.
192. Fleming: Glasgow M. J. **96**:257 (Nov.) 1921.
193. Smith: Arch. Dermat. & Syph. **4**:723 (Dec.) 1921.
194. Stokes: Arch. Dermat. & Syph. **4**:778 (Dec.) 1921.
195. McKenna: Brit. M. J. **2**:473 (Sept. 24) 1921.
196. Gralka: Jahrb. f. Kinderh. **92**:205, 1920.

THE ARSENICAL PREPARATIONS

Chemically identical substances are arsphenamin, arsenobillon, diarsenol (sodium arsphenamin), kharsivan; and neo-arsphenamin, novarsenobillon, neodiarsenol, neokharsivan.[197] Six different brands of arsphenamin studied by Voegtlin and Smith[198] were found to have approximately the same trypanocidal activity. Six different samples of neo-arsphenamin varied in this respect to a slightly greater extent. Schamberg[199] found that though the margin of safety is greater for neo-arsphenamin, arsphenamin itself has greater trypanocidal activity.

In order to secure greater uniformity of these products, the government[200] issued tentative "specifications for arsphenamin," giving the required amount of protection for rats infected with *Treponema equiperdum*. There was virtually unanimity as to the advisability of some such assurance of uniformity, expressed by syphilographers consulted on the subject.

Opinion as to the relative merits of the different arsenicals seems still to be divided. Relative toxicity and relative trypanocidal and therapeutic activity (clinical and serologic), are, of course, the deciding criteria. Queyrat,[201] contrary to many French syphilographers, prefers arsphenamin to neo-arsphenamin, because of the greater rapidity with which a negative Wassermann reaction is obtained; because of the greater pain when some of the solution escapes into the tissues (a useful warning signal), and because of the greater incidence of hepatic reactions with neo-arsphenamin. In the experience of Michelson,[202] the two preparations have about the same action on lesions. He believes accurate comparison to be impossible, owing to individual reactions. Sodium arsphenamin (diarsenol) was found by Michelson and Siperstein[203] to have the same degree of efficacy as the other arsphenamins. According to Wiesenach,[204] tolerance for arsphenamin is increased threefold if injected in a 1 per cent. solution of sodium chlorid. An aqueous solution already alkalized, put up in ampoules under partial vacuum, is now among "new and non-official remedies."[205]

The search for some means of arsenical therapy other than that by the intravenous route is of interest to those treating hereditary syphilis,

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197. Browning: Glasgow M. J. **96**:266 (Nov.) 1921.

198. Voegtlin and Smith: J. Pharmacol. & Exper. Therap. **16**:449 (Jan.) 1921.

199. Schamberg, Kolmer, and Raiziss: Am. J. M. Sc. **160**:25 (July) 1920. See also J. A. M. A. **75**:563 (Aug.) 1920, and ibid. **75**:766 (Sept. 11) 1920.

200. For full description of technic, see Am. J. M. Sc. **160**:25, 1920.

201. Quoted in Editorial, Med. Rec. **100**:597 (Oct. 1) 1921.

202. Michelson: J. A. M. A. **77**:399 (July 30) 1921.

203. Michelson and Siperstein: Arch. Dermat. & Syph. **4**:184 (Aug.) 1921.

204. Wiesenach: Berl. klin. Wchnschr. **5**:845 (July) 1921.

205. Solution Arsphenamin-Lowy, N. N. R., J. A. M. A. **76**:859 (March 26) 1921.

especially if they are unable or unwilling to master intravenous technic. Minet [206] has encountered no persistent hardening nor prolonged pain resulting from small daily subcutaneous injections of neo-arsphenamin when given in 4.7 per cent. glucose to which a little phenol has been added.

The rectal administration of the arsphenamins is championed especially by Wright [207] and by Mehrtens.[208] According to the former, the blood vessels and lymphatics of the rectum and sigmoid convey most of the solution directly to the liver, whence it is distributed to the other tissues. The solution is given very slowly after starvation and enema. According to Wright, the indications for rectal administration are: (1) poor veins; (2) children; (3) hysterical and highly nervous patients. Findlay [191] considers rectal administration of very doubtful value in children because of the fact that the liquid is frequently expelled very quickly.

Among numerous authors who vouch for the efficacy, painlessness and safety of intramuscular sulfarsenol,[209] Dobie [210] maintains that this preparation is ideal for infants and for those with difficult veins.

"Silver arsphenamin" continues to receive favorable comment, especially from the German writers. In a review of the literature on this preparation, Michelson and Siperstein [211] found forty-three German and three English articles. The drug is the sodium salt of silver-diamino-dihydroxy-arseno-benzene;[212] it contains 20 per cent. arsenic and 14 per cent silver. In view of the necessity for prolonged treatment in hereditary cases, it is of interest that, according to Michelson,[202] the therapeutic dose of silver arsphenamin is so small that it is better tolerated over long periods of time. It must be given intravenously,[213] as painful induration results when it is given intramuscularly. Several articles on the use of silver arsphenamin, most of them giving statistics favorable to the drug, have been published.[214]

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206. Minet: Bull. et mém. Soc. méd. d. hôp. de Par. **44**:1475 (Dec. 3) 1920.
207. Wright: New York M. J. **112**:275 (Aug. 28) 1920.
208. Mehrtens: J. A. M. A. **76**:574 (Feb. 26) 1921.
209. Crawford: Glasgow M. J. **96**:263 (Nov.) 1921. Pechère, in discussion of Findlay's paper, Brit. M. J. **2**:197 (Aug. 7) 1920. Tixier and Duval: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:818 (June 3) 1921. Duroeux: Progrès méd. **36**:155 (April 9) 1921. Rawlins.[182]
210. Doble: Lancet **2**:243 (July 31) 1920.
211. Michelson and Siperstein: Arch. Dermat. & Syph. **4**:193 (Aug.) 1921.
212. Fordyce: Arch. Dermat. & Syph. **4**:737 (Dec.) 1921.
213. Mengert: München. med. Wchnschr. **68**:13 (Jan. 7) 1921.
214. Naegeli: München. med. Wchnschr. **67**:1372 (Nov. 26) 1920. Zurhelle: Deutsch. med Wchnschr. **46**:1354 (Dec. 2) 1920. Mouris: Siglo méd. **67**:937 (Dec. 11) 1920. Danysz: Presse méd. **29**:74 (Jan. 26) 1921. Bering: Deutsch. med. Wchnschr. **46**:538 (May 13) 1920. Galewsky: München. med. Wchnschr. **67**:124 (Jan. 30) 1920. Hahn: Deutsch. med. Wchnschr. **46**:92 (Jan. 22) 1920. Scholz: Deutsch. med. Wchnschr. **46**:879, 1920. Parounagian: J. A. M. A. **77**:1706 (Nov. 26) 1921. Walson: Am. J. M. Sc. **161**:418 (March) 1921.

More recent work on the dosage and elimination of the arsenicals indicates that this form of antisyphilitic therapy can probably safely be made more intensive than has hitherto been customary. For example, the Pollitzer method of giving a daily dose of arsphenamin for three doses, followed by mercury injections, has been used without ill effect by both Ormsby [215] and Goodman.[216] Both report better and more rapid results in cases in which the usual method of treatment had failed.

Tollens [217] is most enthusiastic about the Linser method of treatment: i. e., intravenous injections of a neo-arsphenamin-mercuric chlorid mixture. He claims that this method has all the advantages and none of the drawbacks of the other plans of therapy. After two years' experience with a similar method, Zirn [218] also reports excellent results.

THE MERCURCIAL PREPARATIONS

Wassermann [53] believes that mercury is effective mainly because it acts on the cells that have been changed by the poison of the disease, and also on the inversion of lipoid metabolism—thus constituting an antithesis to the arsenic preparations of Ehrlich, which exert a spirillicidal effect. The combined treatment with mercury and arsenic is thus thoroughly logical.

Klecan [219] believes that mercury can and should be given intravenously, and reports prompt symptomatic and serologic results. The salt preferred by Lane [220] for intravenous use is mercury cyanid. His routine is one injection of an arsphenamin substitute and five injections of the cyandid solution per week. Phlebitis occurred in two cases out of 5,000.

Valuable studies on the relative efficiency of the different mercurial preparations in the treatment of hereditary syphilis, are those of Ramsey and Groebner.[221] By quantitative analysis of the elimination of mercury in the urine, they came to the following conclusions: 50 per cent. ointment is to be preferred to the less concentrated forms, and need not be repeated oftener than twice weekly. The quantity absorbed is much increased by friction. Calomel ointment is absorbed less rapidly and to a less extent, and should, therefore, be given in greater concentration. Mercury salicylate in oil should be given hypodermically twice weekly instead of once. Mercuric chlorid, by hypodermic injections, although the dose is very small, continues to be eliminated for six or seven days.

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215. Ormsby: J. A. M. A. **75**:1 (July 3) 1920.
216. Goodman: New York M. J. **112**:494 (Oct. 2) 1920.
217. Tollens: Therap. Halbmonatsh. **35**:212 (April 1) 1921.
218. Zirn: München. med Wchnschr. **67**:1017, 1920.
219. Klecan: Northwest Med. **19**:266, 1920.
220. Lane, J. E.: Lancet **2**:796 (Oct. 15) 1921.
221. Ramsay and Groebner: Am. J. Dis. Child. **20**:199 (Sept.) 1920.

The authors found bichlorid therapy frequently followed by the appearance of protein in the urine, and consider that on that account it should be excluded from the treatment of syphilis in children. Advocates of bichlorid therapy do not admit the validity of this objection. Calomel by mouth is absorbed in small amounts, and continues to be eliminated for a considerable time, so that it is probable that it would be sufficient to give it at intervals of several days, thus avoiding diarrhea. Gray powder is absorbed to a small degree and eliminated rather rapidly, so that large doses, repeated daily, would probably be necessary to maintain mercury in the circulation.

Cole and his associates,[222] studying mercury inunctions, concluded that the only mercury absorbed is that part which is rubbed into the hair follicles and entrances of the sebaceous and sweat glands. Hence all superfluous ointment may be cleansed off immediately after the inunction without lessening the effect. A study of insoluble mercury injections by means of the roentgen ray[223] led to the conclusion that even after four months much of the mercury of gray oil may remain unabsorbed, and that the occasional increase in speed of absorption is capable of producing dangerous cumulative effects.

Hirschberg[224] considers the mercurials indispensable in the treatment of certain gummatous affections of the eye in hereditary syphilis. A special preparation—novasurol—which contains 39 per cent. mercury has been found very effective when given in conjunction with neoarsphenamin.[225] Engel and Türk[187] also vouch for this preparation.

TREATMENT OF NEUROSYPHILIS

There has been much to substantiate, and apparently nothing to disprove, the assertion of Fordyce[113] that the spirochete invades the central nervous system, if at all, during the early general dissemination. Obviously, this is the time for intensive treatment, if neurosyphilis is to be prevented. In all probability the central nervous system in hereditary cases is infected during intrauterine life; so that the only really satisfactory prophylaxis against such a complication is the general one already discussed: treatment of the mother before or during pregnancy. It is, however, safe to say that the earlier treatment is begun and spinal puncture performed in any case of heredosyphilis the less will be the likelihood of development of neurosyphilis. An event which no doubt occurs in hereditary cases (though there have been no reports to that effect) as it has in acquired[226] cases is the development of neurosyphilis

222. Cole, Gericke, and Sollmann: J. A. M. A. **77**:2022 (Dec. 24) 1921.
223. Cole, Littmann, and Sollmann: J. A. M. A. **75**:1559 (Dec. 4) 1920.
224. Hirschberg: Deutsch. med. Wchnschr. **46**:1382 (Dec. 9) 1920.
225. Bruck and Becher: München. med. Wchnschr. **67**:901, 1920.
226. Lakaye: Arch. méd. Belge. **73**:587 (July) 1920; abstr. J. A. M. A. **76**:70 (Jan. 1) 1920.

shortly after thorough treatment with arsphenamin. Moore,[227] however, found that in treated cases, 12.7 per cent. of spinal fluids were positive, as against 25 per cent. in untreated cases. Undoubtedly some such reduction in neurosyphilis can be effected among heredosyphilitics, though treatment must be begun too late in many cases.

Among others, Guy [228] prefers to exhaust intensive general antisyphilitic medication before resorting to intraspinal therapy. Some observers, however, believe that the earlier intraspinal therapy is begun, the greater will be the likelihood of cure of neurosyphilis. Dercum [229] is a strong supporter of "spinal drainage" in the treatment of neurosyphilis. He considers that the withdrawal of spinal fluid during general antisyphilitic treatment is itself a valuable procedure. Stokes and Osborne,[230] comparing cases not receiving spinal drainage with those receiving it, obtained no evidence favoring the drainage method. In both groups, a transient but marked rise in the cell count, followed by a fall, occurred frequently. In their experience, the Swift-Ellis-Ogilvie method of intraspinal treatment (already reviewed by Jeans [1]) produced more satisfactory and gave more permanent results.

Hüsgen [231] says that it is well recognized that nerve tissue absorbs very little mercury, mentioning Serono's attempt to produce a lipotropic mercury compound in cholesterin mercury oleate. The compound studied by Hüsgen was one containing mercury, acetanilid and toluol ("M-A-T"). Though slowly absorbed, it was found in relatively high content in nerve tissue. Its effect on neurosyphilis is not mentioned.

The experimental and clinical investigations of Lafora [232] have convinced him that substances injected intraspinally soon rise to the brain, and that intraspinal therapy is of great benefit in neurosyphilitic processes which have not yet involved the parenchyma. Samovici [233] says that Marinesco has used the arsphenaminized serum technic for ten years, and that he has obtained maximum improvement in incipient syphilitic paraplegia, 50 per cent. improvement in the mania and melancholia forms of general paresis, and virtually no improvement in tabes. Mitchell [234] testifies to the safety and therapeutic value of the Swift-Ellis treatment. Keidel and Moore [235] deny the assertion that the efficacy of intraspinal therapy depends on increased permeability of the meninges, adding that aseptic meningitis produced by irritants may

227. Moore: J. A. M. A. **76**:769 (March 19) 1921.
228. Guy: Arch. Dermat. & Syph. **2**:53 (July) 1920.
229. Dercum: Arch. Neurol. & Psychiat. **3**:230 (March 20) 1920.
230. Stokes and Osborne: J. A. M. A. **76**:708 (March 12) 1921.
231. Hüsgen: Biochem. Ztschr. **112**:1 (Nov.) 1920.
232. Lafora: Rev. neurol. **26**:625 (Aug.) 1919.
233. Samovici: Rév. méd. d. Rosario **11**:138 (July) 1921; abstr. J. A. M. A. **77**:1375 (Oct. 22) 1921.
234. Mitchell: Arch. Dermat. & Syph. **2**:44 (July) 1920.
235. Keidel and Moore: Bull. Johns Hopkins Hosp. **31**:404 (Nov.) 1920.

prove to be an untoward rather than a beneficial factor. Mehrtens [236] warns against any routine system of intraspinal therapy, insisting that each case be treated according to individual requirements.

Excellent results are claimed [237] for intraspinal injections of a hypertonic solution of a minute dose of neo-arsphenamin mixed with the patient's own spinal fluid. In a comprehensive review of intraspinal therapy, Boudreau [238] gives precedence to the Swift-Ellis-Ogilvie method, adding that the mercurialized serum method of Byrnes is more dangerous and produces more severe reactions. He considers that the drainage method of Dercum is not without danger, is extremely painful, and that the results obtained are not in agreement. Sicard [239] claims excellent results in neurosyphilis, with small doses of neo-arsphenamin intravenously, given every day or two.

A study of the nonspecific treatment of neurosyphilis has been made by Mühlens and his associates.[240] It was found that the injection of malarial parasites, or of the spirilla of relapsing fever, produced a favorable effect on the syphilitic infection. Whether this was due to hyperthermia alone or to an immunity reaction was not determined.

Lafora [241] declares that no authentic instance of a permanent cure of paresis or of tabes has ever been published, although the long remissions and periods of improvement often simulate a cure. Contrary to the opinion of Keidel and Moore,[235] Lafora ascribes the benefit from intraspinal therapy to the reactional process in the meninges, which renders the plexus more permeable to drugs given by the vein.

When to consider that a case of syphilis, particularly neurosyphilis, hereditary or otherwise, has been cured, is a question still under discussion. Capurro [242] cites the opinion of Vernes, that if the spinal fluid is normal after provocative injection of an arsenical, and if the negative reaction of the fluid persists for eight months, examinations being made monthly, either the subject never had syphilis, or has completely recovered. Capurro's ten years' experience has produced nothing to conflict with Vernes' findings.

Jacobi,[24] it will be remembered, has denied that reinfection with syphilis is evidence that the disease has been cured. Similarly,

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236. Mehrtens: Colorado M. J. **18**:385 (Nov.) 1920.

237. Ravaut, Arbeit, and Rabeau: Paris méd. **10**:353 (Nov. 13) 1920; abstr. J. A. M. A. **76**:71 (Jan. 1) 1921.

238. Boudreau: Med. Rec. **100**:555 (Sept. 24) 1921.

239. Sicard: Presse méd. **28**:281 (May 8) 1920; abstr. J. A. M. A. **75**:66 (July 3) 1920.

240. Mühlens, Weygandt, and Kirschbaum: München. med. Wchnschr. **67**: 831, 1920.

241. Lafora: Siglo méd. **68**:624 (June 25) 1921; abstr. J. A. M. A. **77**:1375 (Oct. 22) 1921.

242. Capurro: Anal. de la fac. de méd.. Montevideo **5**:562 (Sept.-Oct. 1920; abstr. J. A. M. A. **76**:826 (March 19) 1921.

Goubeau [243] states that a heredosyphilitic may contract the disease de novo, and that it may follow the ordinary course of acquired syphilis. The author is satisfied that the spirochetes still persist in the tissues, but that through a process of adaptation they have become inactive. Fresh spirochetes from without may now prove infectious, and may even add to the gravity of the case. Thus we must accept the idea of superinfection, or, as the author calls it, hypersyphilis. Evidence of the opposite character exists, showing that some heredosyphilitics are wholly, while others are partly immunized.

REACTIONS FOLLOWING TREATMENT

1. *Distribution and Elimination of Arsphenamin and Its Allies.*—Obviously, the method and rate of elimination have much to do with the nature and degree of reaction. Pomaret [244] found that most of the arsphenamin injected intravenously is eliminated very rapidly—much less so by the kidneys than by the intestines (especially through the bile). A very small fraction is eliminated slowly. Simultaneous mercurial treatment retards elimination. These observations have been substantiated by the experimental work of Jeans and Clausen,[245] who found that following an intravenous dosage of 10 mg. per kg. of body weight, 90 per cent. of the arsenic had left the circulation within half an hour. The corpuscles were nearly arsenic free. Penetration of arsenic into the spinal fluid is greatest in cases with evidences of meningeal irritation, and diminishes with the age of the patient, and with each succeeding injection of arsphenamin. After the injection of arsphenamin in kittens, the liver and intestines show the highest arsenic content. Arsenic is practically absent from the brain, skin and muscles. In human subjects five times as much arsenic leaves the body in stools as in urine. The excretion can be detected for two or three weeks. Even at this time, about 50 per cent. of the arsenic remains in the body.

2. *Factors Relating to the Technic.*—There seems to be no question that shaking alkalized solutions of arsphenamin and neo-arsphenamin in the presence of air greatly increases the toxicity.[246] Preparations of neo-arsphenamin which have become difficultly soluble are usually highly toxic even without shaking. The Cologne Arsphenamin Commission [247] concluded that though fatalities are extremely rare in arsphenamin therapy, dosage in excess of the recognized limits of safety plays a very important part in their production. In all cases of dermatitis, and in six out of ten cases of encephalitis, overdosage was

243. Goubeau: Bull. Soc. franç. de dermat. et syph. No. 3, 1920; abstr. Am. J. Syphilis **5**:140 (Jan.) 1921.
244. Pomaret: La Médecine **2**:123 (Nov.) 1920.
245. Jeans and Clausen: Missouri M. J. **19**:43 (Jan.) 1922.
246. Pub. Health Rep. **35**:2205 (Sept. 17) 1920.
247. Deutsch. med. Wchnschr. **46**:299 (March 11) 1920.

shown to be responsible. This commission confirmed the observation that a timid administration or too short courses of treatment may favor the reappearance of central nervous symptoms.

The importance of slow administration of the arsenicals is emphasized by Roth,[248] who found that rapid administration enormously increased toxicity.

Hunt [249] found that not only shaking, but also warming the solution, or allowing it to stand in air, increased the toxicity. Preparing and injecting solutions at low temperature produced no change, though cold may preserve toxicity already present.

3. *Factors Relating to the Drug.*—From the fact that the percentage of reactions is as great in nonsyphilitics as in syphilitics, and from other experimental studies, Strickler [250] concludes that the drug is more likely to be responsible for reactions than the patient. He attributes the majority of reactions to some impurity in the arsphenamin, or to some chemical reaction between the arsphenamin and the chemical constituents of the patient's blood, or to both.

Raiziss and Proskouriakoff [251] state that the impurity causing reactions is present only in very small quantity. In a chemical study of the toxicology of neo-arphenamin, Raiziss and Falkov [252] found that variation in the completeness of substitution in the amino groups (variation in the arsenic-to-nitrogen ratio) accounts for the irregularity of the toxicity and therapeutic effect of neo-arsphenamin. Queyrat [253] urges that manufacturers should be obliged to state on the label the content of the toxic substance—amino-oxyphenyl-arsenoxid. To cite a single example of the importance of such studies, we may mention Cheinisse's report [254] of four crises bordering on asphyxia, in patients given a certain lot of novarsenobenzol, who had previously been given the same drug in large doses without ill effect. Cheinisse quotes Billon's remark that of two samples of the same preparation, the chemist will say one is toxic, and the physiologist the other. Unfortunately, the patient, rather than the rabbit, must often be the test animal.

Contrary to some observers, Pomaret [255] does not believe that arsenoxid is responsible for the symptoms of shock ("nitritoid crisis") produced by some arsenicals, for he found that arsenoxid raises the

248. Roth: Arch. Dermat. & Syph. **2**:292 (Sept.) 1920.
249. Hunt, R.: J. A. M. A. **76**:854 (March 26) 1921.
250. Strickler: Arch. Dermat. & Syph. **2**:692 (Dec.) 1920.
251. Raiziss and Proskouriakoff: Arch. Dermat. & Syph. **2**:280 (Sept.) 1920.
252. Raiziss and Falkov: J. Biol. Chem. **46**:209 (Mar.) 1921.
253. Queyrat: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:446 (April 8) 1921.
254. Cheinisse: Presse méd. **29**:386 (May 14) 1921.
255. Pomaret: Bull. méd., Par. **35**:743 (Sept. 17) 1921.

blood pressure of dogs. In such crises the blood pressure is lowered. Hunt [249] found that this substance is formed when arsphenamin solutions are shaken, warmed, or allowed to stand, and attributes to it the toxic symptoms following such procedures. His observations strongly support the idea that the physical condition (colloidal?) of the solution, or the presence of a very labile toxic compound may, at times, account for untoward reactions.

4. *Factors Relating to the Patient.*—Kolmer and Lucke [256] found that the tissue changes produced by neo-arsphenamin are of the same character as those produced by arsphenamin, but less severe in proportion to the dosage. Tokuda [257] strongly opposes Berman's theory (reviewed by Jeans [1]) attributing untoward reactions to precipitation of serum globulins. He has confirmed the relative increase in globulins, but he attributes untoward reactions either to technical errors in administration or to the presence of impurities in the drug.

The phenomenon of rise in pulmonary pressure following arsphenamin injections has been studied by M. I. Smith [258] and by Jackson and Rapp.[259] The former believes the phenomenon to be due to the mechanical blocking or constricting action of the pulmonary vessels, depending on the amount of alkali used. According to Jackson and Rapp, first class preparations of arsphenamin have no direct action on the bronchial musculature of dogs.

HEPATIC REACTIONS

It has been found [260] that when the liver is damaged by arsphenamin increase in the cholesterol content of the blood is early and marked—a valuable sign of a precarious liver condition in patients under treatment. On account of the high blood urea values frequently found in patients with hepatic reactions, a diet rich in nitrogen is condemned, as is also too free exercise. The suggestion that arsphenamin produces jaundice by rendering the liver more liable to bacterial invasion, has been fairly well discredited by studies in agglutination (Walker) and pathology (Turnbull [261]). It seems far more likely that the effect is direct rather than indirect.

Brocq [262] gives convincing evidence of the dual effect on hepatic tissue of the spirochetes, on the one hand, and of the arsenical spirocheticide, on the other. Cases in which toxic injury of the liver

256. Kolmer and Lucke: Arch. Dermat. & Syph. **2**:289 (Sept.) 1920.
257. Tokuda: Arch. Dermat. & Syph. **4**:512 (Oct.) 1921.
258. Smith, M. I.: J. Pharmacol. & Exper. Therap. **15**:279 (June) 1920.
259. Jackson and Rapp: J. Lab. & Clin. M. **6**:1 (Oct.) 1920.
260. Editorial, J. A. M. A. **75**:543 (Aug. 21) 1920.
261. London Letter, J. A. M. A. **76**:189 (Jan. 15) 1921.
262. Brocq: Bull. méd., Par. **35**:235 (March 19) 1921.

reduces its resistance, thus enabling the spirochetes to damage it further, require the continued administration of arsphenamin. Cases in which toxic injury by the drug is the sole factor, naturally require immediate cessation of arsenotherapy. Katsainos [263] cites Ravaut [264] as showing that when the liver is damaged, its proteopexic ability is abolished, and, albuminous substances passing through unchanged, produce hemolysis in the general circulation. This is caused by many diseases, mostly febrile, and by different chemicals, including arsphenamin. In a recent article, Milian [265] restates his opinion (reviewed by Jeans [1]) that the icterus is due to the syphilitic infection, and that treatment should be continued, or if it has been discontinued it should be begun again.

Interesting case reports of hepatic reactions, with necropsy findings in some of the fatal cases, are given by Foulerton,[266] Silbergleit and Föckler,[267] and Todd.[268] The relative frequency of such reactions in the winter months is noted in the two articles last named.

CUTANEOUS REACTIONS

Moore and Keidel [269] report twenty-three cases of the dermatitis group of reactions. Of the eighteen severe reactions, five were fatal (27.7 per cent.). The authors believe that the reactions were anaphylactic in origin. Three cases of dermatitis of the lichen ruber type are reported.[270] Discussions and case reports of dermatitis exfoliativa following arsenotherapy have been presented by several authors (Whiteside,[271] French,[272] Stuart and Maynard [273]).

The strong probability of the anaphylactic nature of such reactions calls to mind the suggestion [274] that drug reactions may depend on the formation of compounds between the drug and the body proteins, so that what amount to foreign proteins are formed. It is also noteworthy that Auer [275] has demonstrated that anaphylactic reactions may be caused in the skin by substances which themselves do not

263. Katsainos: J. A. M. A. **76**:195 (Jan. 15) 1921.
264. Ravaut: Presse méd. **28**:893 (Dec. 11) 1920.
265. Milian: La Médecine **2**:113 (Nov.) 1920.
266. Foulerton: Brit. M. J. **1**:864 (June 26) 1920.
267. Silbergleit and Föckler: Ztschr. f. klin. Med. **88**:333, 1919; abstr. J. A. M. A. **75**:1300 (Nov. 6) 1920.
268. Todd: Lancet **1**:632 (March 26) 1921.
269. Moore and Keidel: Arch. Int. Med. **27**:716 (June 15) 1921.
270. Buschke and Freymann: Med. Klin. **17**:899 (July 24) 1921; abstr. J. A. M. A. **77**:1215 (Oct. 8) 1921.
271. Whiteside: Northwest Med. **20**:153 (June) 1921.
272. French: Lancet **1**:1262 (June 12) 1920.
273. Stuart and Maynard: Arch. Int. Med. **26**:511 (Nov. 15) 1920.
274. Editorial, J. A. M. A. **75**:1070 (Oct. 16) 1920.
275. Auer: J. Exper. Med. **32**:427 (Oct.) 1920.

produce anaphylaxis. Stuart and Maynard,[273] in reporting their case, noted that cutaneous hypersensitiveness to arsphenamin and neoarsphenamin occurs in patients who have suffered from exfoliative dermatitis. Strickler [276] showed that arsphenamin given intravenously can stimulate the production of a luetin test in nonsyphilitic patients, as well as a positive Pirquet test, previously negative. Cutaneous tests for food sensitization were not affected by arsphenamin.

With regard to silver arsphenamin, Stühmer [277] reports the occurrence of numerous cases of dermatitis following the use of the drug; and Lochte [278] reports a case of argyria.

REACTIONS REFERABLE TO THE CENTRAL NERVOUS SYSTEM

Though Herxheimer (focal) reactions to arsenotherapy may occur anywhere, as in the liver or intestine,[279] it is in the central nervous system that such reactions are most likely to be dangerous. Such focal reactions are given diagnostic value by Speroni,[280] who considers them analogous to focal reactions to tuberculin in cases of tuberculosis.

Epileptiform seizures [281] and neuroretinitis [282] have also been reported—plausible reasons being given in each case for considering the therapy responsible, rather than the disease itself.

With regard to reactions to intraspinal treatment, fever, nausea, vomiting and pains following shortly after injections, occur so frequently that relatively little consideration is given them. In most cases, the advantages of the treatment far outweigh such disadvantages. Occasionally, however, more severe reactions are noted. In one case,[283] complete paralysis of the legs, with incontinence of urine and feces, followed the fourth intraspinal injection. The paralysis improved. Jacobi [284] reports two fatalities following endolumbar injection of sodium arsphenamin by Gennerich's technic. Necropsy showed severe irritation, with hemorrhages in the pia. In one case of cerebrospinal syphilis treated intraspinally by Keidel and Moore,[285] the first injection

276. Strickler: Arch. Dermat. & Syph. 4:177 (Aug.) 1921.

277. Stühmer: München. med. Wchnschr. **67**:836, 1920.

278. Lochte: Therap. Halbmonatsh. **34**:334 (June 15) 1920; abstr. J. A. M. A. **75**:1168 (Oct. 23) 1920.

279. Herxheimer: Berl. klin. Wchnschr. **57**:369, 1920.

280. Speroni: Sémana méd. **28**:725 (June 23) 1921; abstr. J. A. M. A. **77**:1057 (Sept. 24) 1921.

281. Bejarano: Siglo méd. **67**:302 (April 24) 1920; abstr. J. A. M. A. **75**: 278 (July 24) 1920.

282. Oden and White: Am. J. Ophth. **4**:365 (May) 1921.

283. Aldabalde: Siglo méd. **68**:285 (March 19) 1921; abstr. J. A. M. A. **76**:1619 (June 4) 1921.

284. Jacobi, W.: Therap. Halbmonatsh. **35**:307 (May 15) 1921; abstr. J. A. M. A. **77**:1059 (Sept. 24) 1921.

285. Keidel and Moore: Am. J. M. Sc. **162**:209 (Aug.) 1921.

was thought to have set up an aseptic meningitis, with partial occlusion of one or more foramina of exit from the fourth ventricle, and resulting internal hydrocephalus. This danger from intraspinal therapy is characterized as "possible though remote."

MISCELLANEOUS REACTIONS

Among the miscellaneous reactions reported are (1) two cases of aplastic anemia (in women);[286] (2) a case of stomatitis with aplastic anemia (fatal) which the authors[287] considered related to the dermatitis exfoliativa type of reaction; (3) a case of hemorrhagic purpura[288] which was considered to be similar in nature to the cases of epileptiform convulsions following injections, in which post mortem examination shows punctate hemorrhages in the brain, attributable to damage of capillary epithelium by the remedy. Lesne[289] reports a case in which the fourth dose of neo-arsphenamin (following three well tolerated doses) was followed by anuria and acute uremia, with death on the eighth day. A case with nitritoid crises accompanied by transient myopia and albuminuria is reported by Milian and Périn.[290]

According to Gougerot,[291] the causes of late reactions to the arsenicals are (1) arsenical lesions of the viscera, (2) recurrence of "unextinguished" syphilis, (3) "tertiarization," i. e., increase in destructive tendency of the lesions.

REACTIONS TO MERCURY

Such common reactions as salivation, diarrhea, renal damage, etc., have been discussed fully and allowance has been made for them in the various plans of treatment. Klauder and Kolmer[71] cite clinical and experimental observations to show that mercury is considerably more nephrotropic than arsphenamin or neo-arsphenamin. In intensive treatment with both mercury and the arsenicals, the nephrotropic action of mercury may retard the elimination of arsenic, and in this way cause untoward effects of arsenic (an opinion concurred in by Pomaret[244]). Such conjoined intensive treatment is, therefore, not advised. Two fatal cases of stomatitis due to mercury are reported.[292] One patient died following involvement of the facial bones. The other had extensive necrosis of the mandible.

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286. Gorke: München. med. Wchnschr. **67**:1226 (Oct. 22) 1920.
287. Moore and Keidel: Arch. Dermat. & Syph. **4**:169 (Aug.) 1921.
288. Anwyl-Davies: Brit. J. Dermat. & Syph. **33**:264 (July) 1921.
289. Lesne: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:399 (March 18) 1921; abstr. J. A. M. A. **76**:2433 (May 21) 1921.
290. Milian and Périn: Paris méd. **11**:388 (Nov. 12) 1921.
291. Gougerot: La Médecine **2**:119 (Nov.) 1920.
292. Gérard-Maurel and Rénard: Rev. de stomatol. **22**:12 (Dec.) 1920.

PREVENTION AND TREATMENT OF REACTIONS TO ARSENOTHERAPY

The foregoing consideration of toxicology and of toxic reactions naturally contains many implicit suggestions for the prevention of such reactions. Certain additional observations should be mentioned, as having a more direct bearing upon the prophylaxis and treatment of these conditions. Working with mice, Kolle [293] found that a small intravenous dose of arsphenamin furnished perfect protection against a fatal dose of the same drug injected twenty-four hours later. This furnishes an experimental basis for the clinical custom of giving small doses at the start of a course of treatment. Lake [294] notes a definite decrease in toxicity if alkali is added up to 30 per cent. in excess of the amount necessary to form the disodium salt of arsphenamin. Neutralization as ordinarily carried out goes to a point midway between the monosodium and the disodium salts.

Busman [295] studied cases of repeated acute reactions, usually considered personal idiosyncrasies to the drug. The observation of Stokes that atropin and induced anaphylaxis are of value in treating the condition, was confirmed by the author. Both dividing the dose and preceding it by atropin are of greater value than either method alone, and may be the means of permitting patients to take the drug who might otherwise be deprived of it. Sicard [296] advises limiting the shock reaction to one limb by applying a constricting band to the root of the limb into which the injection is made, slowly removing this five minutes later. Two patients constantly presenting severe nitritoid crises after every injection of neo-arsphenamin, were tided past the danger point by this simple method. The procedure is called "arsenical anticlasis by topophylaxis." There was never any sign of local flocculation or precipitation in these cases.

Cheinisse [297] strongly recommends Sicard's preliminary injection of 30 c.c. of physiologic solution of sodium chlorid containing 0.6 or 0.75 gm. sodium carbonate. The arsenical is injected through the same needle. Even after the appearance of arsphenamin shock, the immediate injection of 10 c.c. of a 10 per cent. solution of sodium carbonate may abort it. Other methods considered are: addition of 3 or 4 drops of ether to the arsenical (Kopaczewski); dissolving the arsenical in 20 per cent. solution of saccharose; injecting 3 c.c. of ether subcutaneously ten minutes before the arsenical; injecting 5 c.c. camphorated

293. Kolle: Med. Klin. **16**:355 (April 4) 1920.
294. Lake: Am. J. Syphilis **5**:96 (Jan.) 1921.
295. Busman: J. A. M. A. **76**:1302, 1921.
296. Sicard, Paraf, and Forestier: Bull. et mém. Soc. méd. de hôp. de Par. **45**:775 (May 27) 1921.
297. Cheinisse: Presse méd. **29**:506 (June 25) 1921.

oil half an hour before it. Sicard and Paraf [298] consider that sodium carbonate is of value as preventing flocculation. Milian, discussing their paper, said that he uses sodium hydroxid in much the same way, but believes that it acts by preventing the splitting up of the arsenical, which is responsible for the nitritoid crises in connection with suprarenal insufficiency. Queyrat [253] urges, in case of mishap, prompt venesection, and instillation, by the drip method, of 1,000, or 1,500 c.c. physiologic solution of sodium chlorid with glucose. He also advises that epinephrin be given daily, up to 5 or 6 mg. Lumbar puncture is also required, but the main indication is to give mercurial treatment to check the action of the disease on the nervous centers. Gastou [299] advises that the urine be examined before every injection, especially for the presence of albumin and bile pigments. He adds that a solution of epinephrin should always be at hand.

The conclusion of Strickler,[300] that neither atropin nor epinephrin prior to arsphenamin injections has any influence on early reactions, is of considerable interest.

Two fatal cases of cerebral reaction reported by Hitch,[301] in which widespread capillary hemorrhages were found, lend support to Dudley's theory that anoxemia caused by interalveolar hemorrhage has much to due with reactions. On this account, the continuous administration of oxygen is urged as the only hope in such cases. Ross [302] is an advocate of preliminary administration of atropin.

To obviate the annoying "lumbar puncture headaches," Baar [303] gives salt solution intravenously, following each lumbar puncture. In a series of fifty punctures, only three headaches followed the use of this method.

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298. Sicard and Paraf: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:11 (Jan. 14) 1921; abstr. J. A. M. A. **76**:897 (March 26) 1921.

299. Gastou: Bull. med., Par. **34**:954 (Oct. 30) 1920; abstr. J. A. M. A. **76**:71 (Jan. 1) 1921.

300. Strickler: New York M. J. **112**:498 (Oct. 2) 1920.

301. Hitch: Lancet **1**:1311 (Jan. 19) 1920.

302. Ross: Northwest Med. **21**:63 (March) 1921.

303. Baar: Med. Rec. **98**:598 (Oct. 9) 1920.

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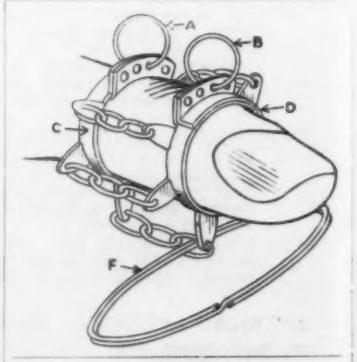

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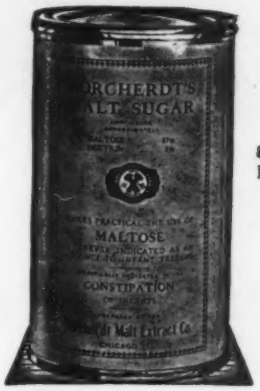

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